GUIDELINES

HIV Palliative Care

A publication of the Southern African HIV Clinicians Society

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ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immune Deficiency Syndrome
APACHE	Acute Physiology and Chronic Health Evaluation
ART	Antiretroviral Therapy
ARV	Antiretroviral
BMI	Body Mass Index
cART	Combination Antiretroviral Therapy
CBD	Cannabinoid-Drug
CBM	Cannabinoid-Based Medicine
CCM	Cryptococcal Meningitis
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CNS	Central Nervous System
CM, CCM	Cryptococcal Meningitis
DALY	Disability-Adjusted Life Years
DILI	Drug-Induced Liver Injury
DOH	Department of Health
FBC	Full Blood Count
FS	Free State
HAD	HIV-Associated Dementia
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPCA	Hospice Palliative Care Association
IDSA	Infectious Diseases Society of America
INR	Immune Non-Responder
IRIS	Immune Reconstitution Inflammatory Syndrome
KS	Kaposi's Sarcoma
KZN	KwaZulu-Natal
LFTs	Liver Function Tests
LMICs	Low and Middle-Income Countries
MAI/MAC	*Mycobacterium Avium (Intracellulare)* Complex
MRA	Magnetic Resonance Angiogram
MRI	Magnetic Resonance Imaging
MDR	Multi-Drug Resistant
M&E	Monitoring and Evaluation
MP	Mpumalanga
NADCs	Non-AIDS-Defining Cancers
NCD	Non-Communicable Diseases
NDOH	National Department of Health
NEML	National Essential Medicines List
NGO	Non-Governmental Organisation
NSAID	Non-Steroidal Anti-Inflammatory Drug
NW	North West (Province)
PHC	Primary Health Care
PJP	*Pneumocystis Jiroveci* Pneumonia
PNS	Peripheral Nervous System

PPC	Paediatric Palliative Care
RCT	Randomised Controlled Trial
REE	Resting Energy Expenditure
RICP	Raised Intracranial Pressure
SA	South Africa
SJS	Stevens Johnson Syndrome
SLE	Systemic Lupus Erythematosus
TB	Tuberculosis
THC	Tetrahydrocannabinol
U&E	Urea and Electrolytes
UNAIDS	Joint United Nations Programme on AIDS
US	United States
VACS	Veterans Aging Cohort Study
VL	Viral Load
WHO	World Health Organization
WHPCA	Worldwide Hospice Palliative Care Alliance
5-HT3	5-Hyroxytryptamine (serotonin)

Palliative Care Guidelines for the Management of HIV-Infected People in South Africa

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for the Southern African HIV Clinicians' Society Guidelines Committee

Box 1. **What is Medicine?**

> **"**First I will define what I conceive medicine to be. In general terms, it is to do away with the sufferings of the sick, to lessen the violence of their diseases, and to refuse to treat those who are overmastered by their disease, realizing that in such cases medicine is powerless.**"** Hippocrates, c460-370 BCE
>
> Quoted in Shaner DM. Suspending Ethical Medical Practice. *N Engl J Med* 2010; 363: 1988

1. INTRODUCTION

1.1 What is palliative care?

Definition 1. The National Policy Framework and Strategy Policy on Palliative Care, Department of Health, South Africa, 2017-2022: 'Palliative care is a multidisciplinary approach to the holistic care and support of patients and families facing a life-threatening illness. Its aim is to improve quality of life while maintaining dignity from diagnosis to death. For children, the spectrum of illness includes life-limiting conditions that may progress to death or may be severely disabling. Palliative care should be available to all patients *as* needed, *from birth until death,* and should be accessible at all levels of the health care service. Palliative care cuts across all health programmes in the delivery of services'.[1]

Definition 2. The World Health Organization (WHO): 'Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention, treatment and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial or spiritual". Palliative care:

- Affirms life and regards dying as a normal process.
- Neither hastens nor postpones death.
- Provides relief from pain and other distressing symptoms.
- Integrates the psychological and spiritual aspects of patient care.
- Offers a support system to help patients live as actively as possible until death.
- Offers a support system to help the family cope during the patient's illness and during the experience of bereavement.' [2]

Definition 3. End-of Life Care: This refers to health care, not only of a person in the final hours and days of their life, but more broadly care of those with a terminal condition that has become progressive and incurable. (Wikipedia, accessed October 7, 2018) The National Council for Palliative Care, United Kingdom, states that end-of-life care is given to persons "likely to die within 12 months". Several commentators make the point that end-of-life care is not identical to palliative care, i.e. end-of-life care is a final phase within the broader provision of palliative care. Nonetheless, its starting point is sometimes difficult to identify.

The principal goal of palliative care is the relief of suffering. This is done through individualising care – addressing symptoms, controlling pain, listening to the patient, responding to fear and anxiety, incorporating families and the patient within a competent, professional and resourceful team, and bereavement support for the patient's loved ones. A defining characteristic of palliative care is the notion of ***total pain***, the recognition that pain cannot be alleviated completely unless all contributing parts that inform the patient's life-experience are addressed. Palliative care is ***team work*****.** The team comprises a range of medical, nursing, para-medical and psychosocially-trained health and community workers. The leader is usually a senior palliative care-trained clinician. The South African National Policy Framework on Palliative Care envisages that these teams will be accessed by patients – including those who are Human Immunodeficiency Virus (HIV)-positive – at the community, district and regional levels in free-standing clinics and at all district, secondary and tertiary-level hospitals across the country. These proposals are currently aspirational, however, as significant barriers to implementation still lie ahead: approval and financing, recruitment and staffing, education and training, etc.

The individual matters. The process of palliative care is just, non-judgmental and given to all irrespective of colour, creed or class. "The relief of suffering is considered one of the primary ends of medicine by patients and the general public."[3] Yet patients and their families do not necessarily agree with health workers on the means to this end. "In the care of the dying, patients and their friends and families do not divide suffering into its physical and nonphysical sources the way doctors, who are primarily concerned with the physical, do." Palliative care recognises this divide and addresses it by taking all causes of suffering into account when aligning the goals of the patient with that of the caregiver and health care system. A consultative, multi-disciplinary approach forms the basis of this model of care.

2. THE HIV EPIDEMIC IN SOUTH AFRICA (SA) IN 2018, PALLIATIVE CARE: DEFINING THE NEED

2.1 HIV Morbidity and Mortality

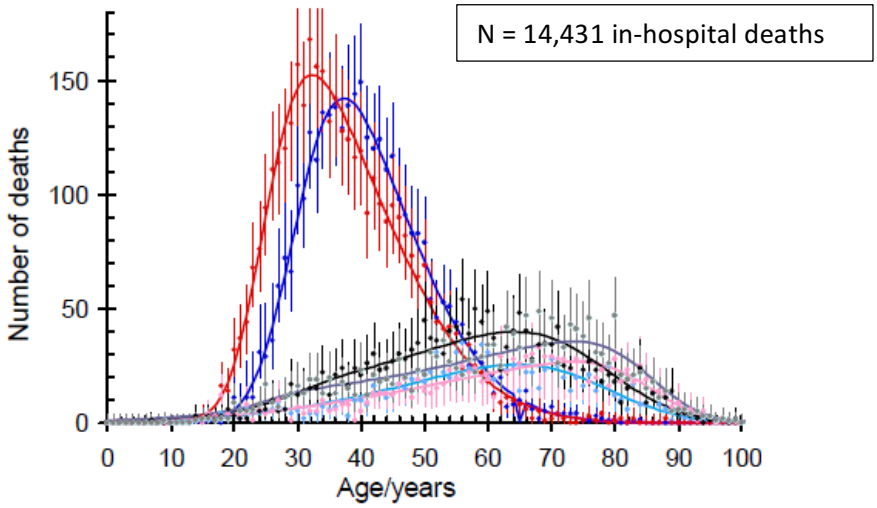
The Joint United Nations Programme on HIV and AIDS (UNAIDS) reported in 2016 that 7.1 million (range, 6.4-7.8 million) South Africans were HIV-positive.[4] It was estimated that 56% (range, 50-61%) were on antiretroviral therapy (ART) yet viral control could only be confirmed in 45% (range, 41-50%). Although 95% of pregnant women had accessed ART, mother-to-child transmission of HIV in 2016 still resulted in 12,000

newborn infections (range, 9,600-22,000). The 2017/2018 SA Human Sciences Research Council's (HSRC) report, released in July 2018, estimates that 7.9 million South Africans are now living with HIV, an increase of 1.6 million over the past five years, 70.6 percent are taking ART and 87.5 percent of PLHIV aged 15-64 on ART have suppressed viral loads. The number of new cases among females aged 15-24 years has remained high since 2012 and is *three times* that of their male peers while the overall prevalence of HIV among South Africans was 14%. Prevalence rates were highest in the provinces of KwaZulu-Natal (KZN), at 18.1%, and Mpumalanga (MP), the Free State (FS) and the Eastern Cape (EC), with rates of 17.3, 17.0 and 15.3, respectively.[5] Notwithstanding these numbers, new HIV infections have fallen by 44% since 2012 and HIV testing has been on the rise.

The evolution of the South African epidemic has meant that many who are infected yet undiagnosed and ART naïve, or who have defaulted on ART in the past, now present to hospitals and clinics with symptomatic disease viz. the HIV-sick. It's estimated that as many as 40-60% of the medical beds in the public hospitals in KZN, Gauteng, MP and FS are occupied by the HIV-infected.[6, 7]

Few, if any, state hospitals offer a formal palliative care service and despite access to ART since 2005, mortality from HIV-related disease remains high. Of the 14,431 patients who died in Soweto's Chris Hani Baragwanath Hospital from 2006 to 2009, 64% of the men and 82% of the women were HIV-infected. More than 90% of those dying between the ages of 30-40 years, were infected.[8]

Figure 1. The Number of Deaths by Age and HIV-Status of Men and Women Admitted to the Chris Hani Baragwanath Hospital, Soweto, 2006-2009[8]



Legend: Red: HIV-infected women; Pink: HIV-uninfected women; Blue: HIV-infected men; Light blue: HIV-uninfected men; Black: HIV-status unknown (males); Gray: HIV-status unknown (women)

2.2 Causes of Death of Hospitalised HIV-Sick in South Africa

A small but well analysed autopsy group from the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is reported in Table 1.[9] The dominant regional pathogen of

the HIV-infected is *Mycobacterium tuberculosis.* All who died of TB had disseminated infection at the time of their death. The first 90 days following the start of ART, viz. 'early-ART', is a key risk period for death from TB, yet a recovering immune system has been implicated in these deaths viz. the immune reconstitution inflammatory syndrome (IRIS).[10]

Table 1. Causes of Death at Post-Mortem Examination of 39 HIV-Infected Patients of the Charlotte Maxeke Johannesburg Academic Hospital, January-December 2009[9]

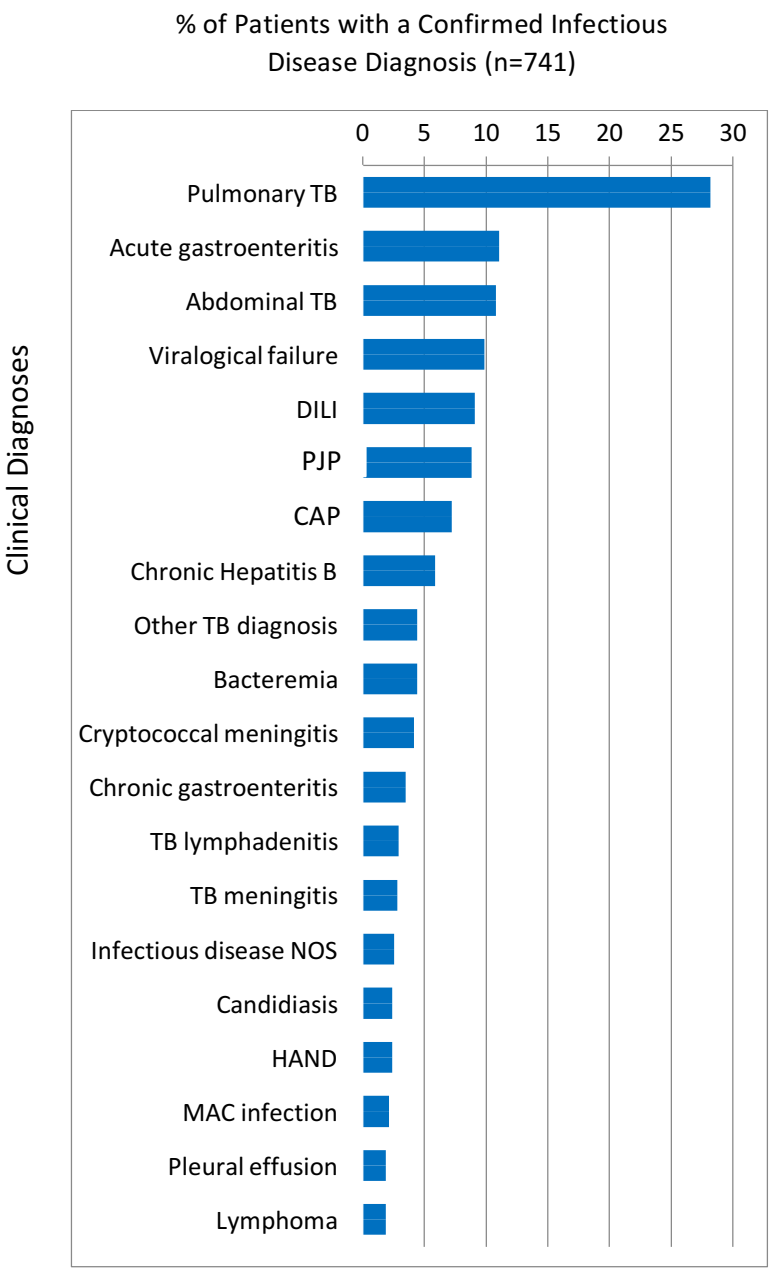
Causes of death by category and/or organism[a]	All deaths (n=39)	Pre-ART deaths (n=14)	Early-ART deaths (n=15)	Late-ART deaths (n=10)
Mycobacterial, n (%)	27 (69%)	8 (57%)	13 (87%)	6 (60%)
Bacterial, n (%)	13 (33%)	5 (36%)	6 (40%)	2 (20%)
Fungal, n (%)	8.2 (21%)	3 (21%)	4 (27%)	1 (10%)
Viral, not HIV, n (%)	3 (8%)	2 (14%)	0 (0%)	1 (10%)
Neoplasm, n (%)	10 (26%)	3 (21%)	3 (20%)	4 (40%)
Organ dysfunction[b], n (%)	10 (26%)	1 (7%)	5 (33%)	4 (40%)
IRIS, n (%)	11 (28%)		11 (73%)	
Diagnosis unsuspected at death[c], n (%)	19 (49%)	7 (50%)	8 (53%)	4 (40%)
Unexplained, n (%)	5 (13%)	4 (29%)	1 (7%)	0 (0%)

Legend: Categorised by the duration of ART at the time of death. Pre-ART deaths occurred in patients who were HIV-positive and eligible for ART but had not yet received it (CD4 cell count <200 cells/mm^3) or those who had received <7 days of ART. Early-ART deaths occurred between 7-90 days of ART. Late-ART deaths occurred after >90 days of ART.

a. All causes of death (immediate and contributing) are included and each patient may have ≥1 cause of death
b. Non-infectious organ dysfunction, i.e. pulmonary embolism or end-stage renal disease
c. At least one cause of death was revealed only through the post-mortem investigation

Figure 2 summarises the admission-diagnoses of 741 patients evaluated during a 6-month period on the Infectious Diseases consultation service of the Helen Joseph Hospital, a public hospital in Johannesburg of which ninety-three percent of the patients were HIV-infected. The individual bars demonstrate the wide variety of conditions that affect the acutely sick. Although TB is the most frequent diagnosis, it is one of *many* life-threatening conditions in this group of patients. Note that virtually all these conditions are treatable and the majority can be cured.[11]

Figure 2. Medical Diagnoses of a Six-Month Review of In-Patient Infectious Disease Consultations at the Helen Joseph Hospital, Johannesburg, 2015-2016[11]



Data Analysis of a Six-Month Review of In-Patient Consultations on the Infectious Diseases Service of the Helen Joseph Hospital, 2015-2016.

N=741 patients of whom n=691 were HIV-positive viz. 93% of those whose HIV status was tested and known.

Of the 20 most typical infection-related consultations, TB in a variety of its manifestations was the most common. Nevertheless, this list of diagnoses illustrates the wide range of additional conditions that lead to the HIV-sick seeking hospitalisation in South Africa's public sector.

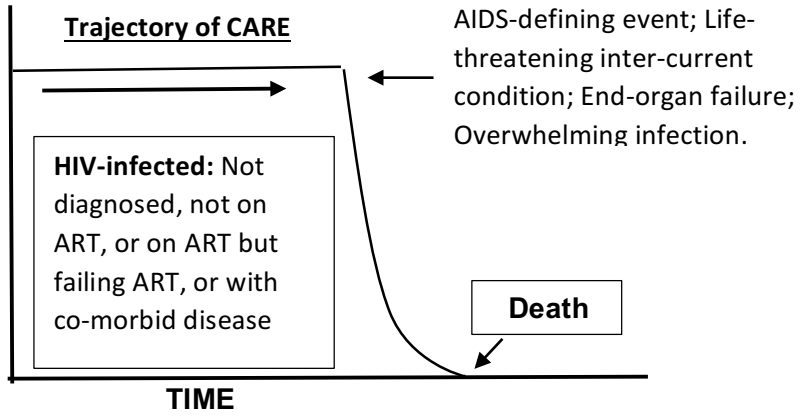
Abbreviations: TB=Tuberculosis; DILI = Drug-Induced Liver Injury; PJP= *Pneumocystis Jirovecii* Pneumonia; CAP = Community-Acquired Pneumonia, NOS=Not Otherwise Specified; HAND = HIV-Associated Neurocognitive Disorder; MAC = *Mycobacterium Avium* Complex.

3. MODELS OF HIV-PALLIATIVE CARE, ADDRESSING THE NEED

Models of palliative care vary. Three models that are frequently encountered by the HIV clinician in SA are briefly discussed in this section.

3.1 No Formal Palliative Care Provided

Figure 3. The HIV-Infected Patient, No Palliative Care



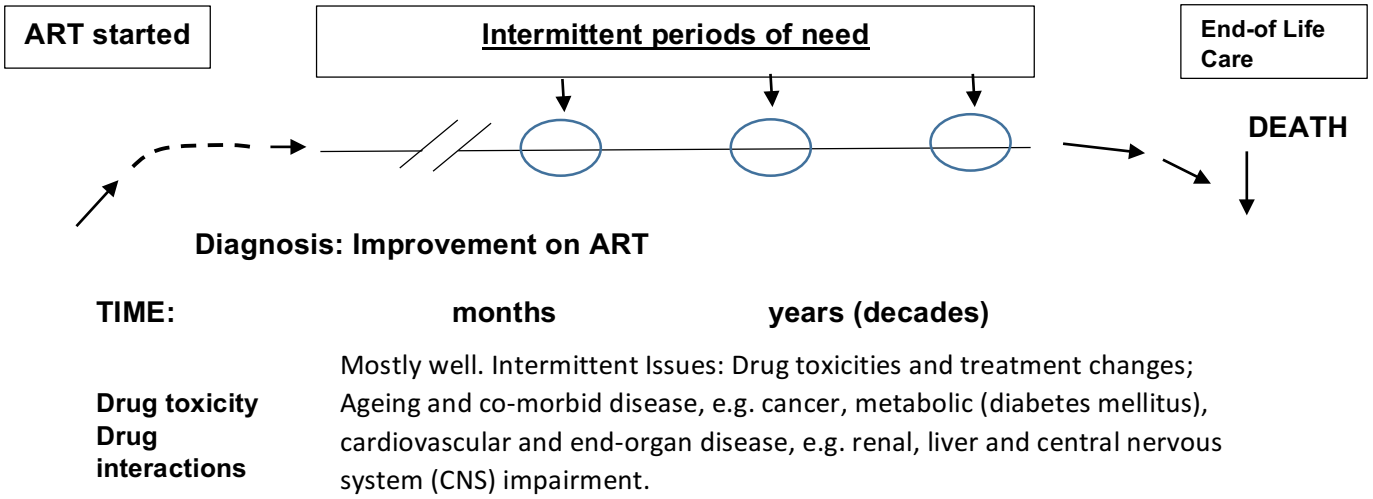
Legend: This model is adapted from original sources[12, 13]

In this model (Figure 3) little or no palliative care is accessed prior to death. The HIV infection is not well controlled or is undiagnosed prior to admission, though the patient has been admitted to hospital acutely ill. Although the risk of death is often high, palliative care is not offered nor integrated with acute care. Suffering is not adequately relieved and patients and their families often feel abandoned by the public health care system. This model of care is the usual experience of the HIV-sick at this time in SA (for additional comments see Appendix A).

3.2 Intermittent Palliative Care Given During Periods of Need: The HIV-Infected Patient on ART with Long-Term Viral Control and Immune Reconstitution

In this model, the patient on ART initially improves but requires assistance to cope with drug toxicities and possible drug interactions. As time goes by, the need for both acute curative and palliative care is encountered during periods of serious co-morbid disease, failure of ART, re-introduction of active ART, and finally, during special health needs towards the end of life.[14] (see Figure 4). Illness increases in importance and frequency with the ageing of HIV survivors as does its complexity and costs.

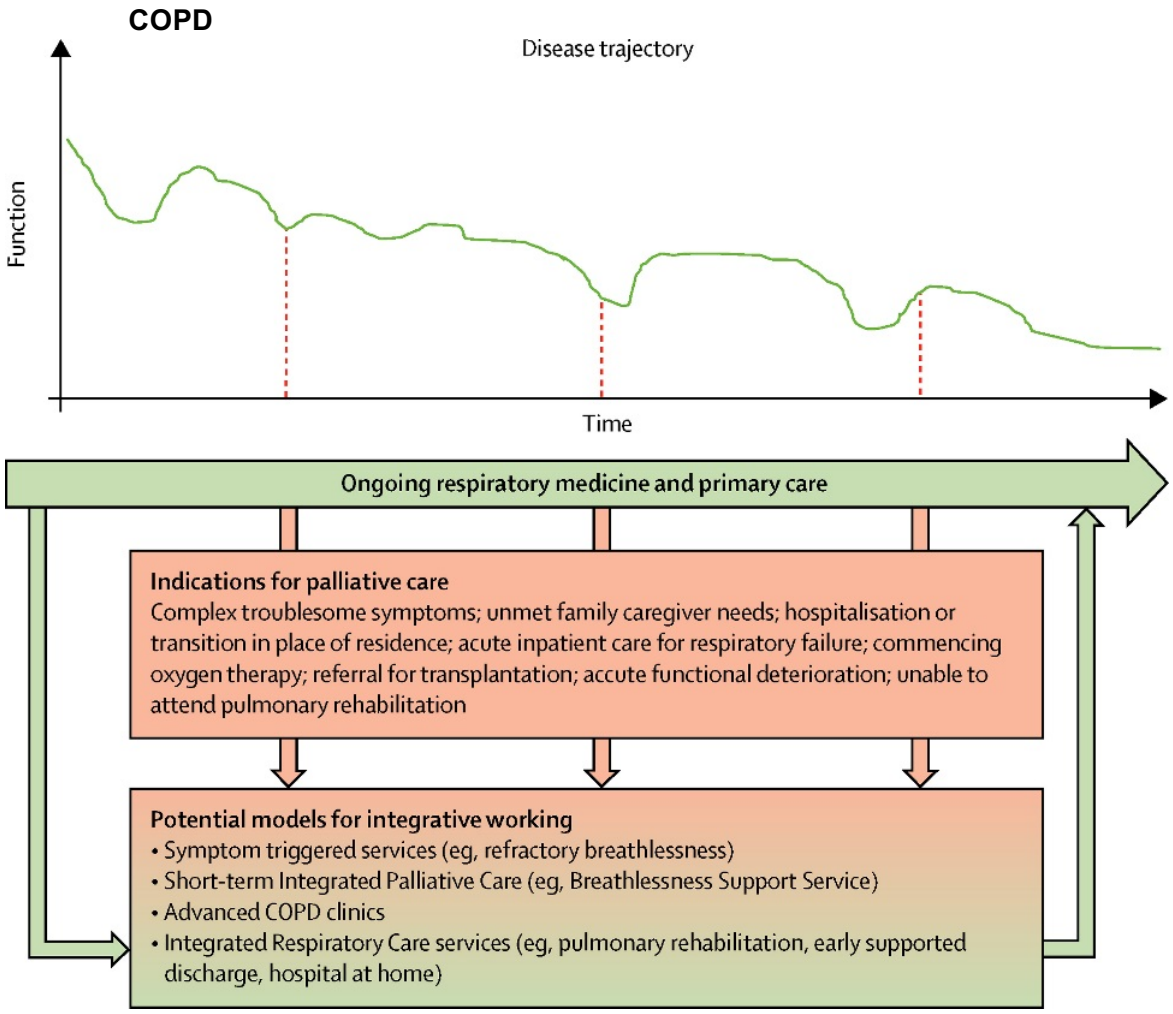
Figure 4. Palliative Care During Periods of Need



3.3 Integrated Palliative Care for People with Progressive Co-Morbid Disease

Chronic lung disease (CLD) is a problem for long-term survivors of HIV-infection.[15, 16] Infection from birth, inadequate or intermittent viral control and inter-current respiratory tract infections characterise a group of adolescents with advanced and irreversible small airways disease.[17, 18] CLD also affects HIV-infected adults on ART, many of whom are smokers, often men and frequently domicile in high-income countries.[19] In this model of HIV, people with an active co-morbid condition such as chronic obstructive pulmonary disease (COPD), chronic renal failure, heart disease etc., experience a slow but progressive downhill trajectory. Each new episode of disease/hospital admission compromises organ function further and moves the patient towards the end of life.[20] The model in Figure 5 also applies to other chronic diseases experienced by the HIV-infected viz. non-AIDS-defining cancers, progressive neurocognitive impairment, autoimmune conditions and bone and joint disease.

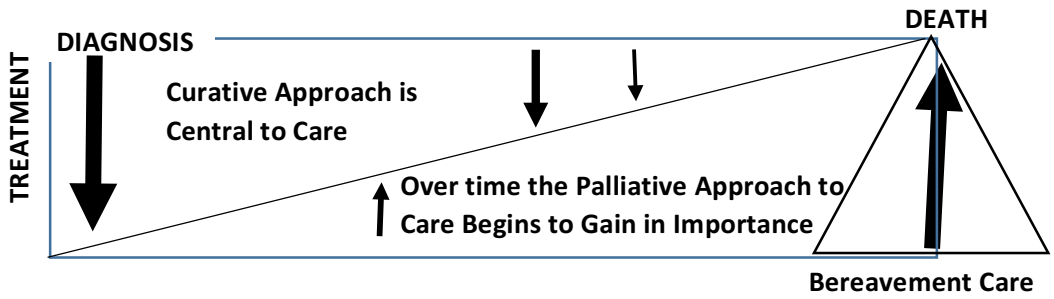
Figure 5. Integrated Palliative Care for People with Progressive Co-Morbid Disease, e.g. Chronic Obstructive Pulmonary Disease (COPD)[19]



3.4 The Traditional Palliative Care Model: From Diagnosis to Bereavement[1]

Palliative care is a continuum of care that starts from the time of diagnosis of a life-threatening illness/condition, e.g. AIDS, and continues until a time after death when bereavement support is provided to the family members of the deceased.[1] During this period, emphasis gradually moves from the curative to the palliative, as dictated by the changing needs of the patient and family (see Figure 6).

Figure 6. Current Concept of Palliative Care: From Diagnosis to Bereavement[1]



Patients on ART who regain normal or near-normal immune activity and whose viral count is 'undetectable', i.e. VL <40-50 copies/mL, have life expectancies similar to that of their uninfected peers.[21] While the availability of ART has brought great benefit, many still unfortunately die. Under normal circumstances, the clinician's mandate is the restoration of a patient's health and wellbeing which begins with obtaining a medical history, the examination of the patient, the formulation of a probable diagnosis, investigation, the start of remedial therapy, the monitoring of the response, a review of laboratory/radiographic data and the confirmation of the diagnosis. Patients want and need to *feel* better and good symptom control is the shared ground of curative and palliative medicine. It addresses the immediate needs of those who suffer. A recent randomised controlled trial (RCT) of palliative care in patients with advanced non-small-cell lung cancer found that this intervention reduced depression, improved quality of life and produced a short but significant 3-month survival advantage.[22]

4. ELIGIBILITY FOR HOME AND HOSPICE SUPPORT, ASSESSING NEED

4.1 Comment

For most, ART preserves and restores immune function and permits survival. However, in every HIV clinic, a small group of patients fail to reconstitute CD4 cells despite ART and viral control. These "immune non-responders" (INRs) are often older (>45 years), start ART late, begin ART at a very low CD4 nadir/baseline viz. <100 cells/mm^3 and give past medical histories that suggest advanced immune suppression viz. previous TB, recurrent bacterial and other infections and unexplained weight loss.[23] Despite adherence to therapy, INRs remain at an increased risk of disease and death notwithstanding years of documented viral suppression.[24] No dependable treatment currently reconstitutes the blood compartment with CD4 cells in this group of patients. Attempts to address this situation by changing background ART in those who are virologically suppressed have not been successful and in the main is discouraged. Where the patient's usual medication may be at fault, e.g. AZT or trimethoprim-sulfamethoxazole, alternative drugs should be tried.

Prevention, such as commencing ART as soon as possible after the start of HIV infection when CD4 cells are likely to be abundant and the thymus functional, is the therapeutic safeguard against immune non-response to ART.[25]

In addition to this group, are those HIV-infected with identifiable causes of immune suppression, e.g. steroid use, alcohol abuse, herbs such as the "African potato", cancer chemotherapy, infections such as TB and *Mycobacterium avium* complex (MAC), malignancies and rheumatological conditions such as Systemic Lupus Erythematosus (SLE), Rheumatoid arthritis and the drugs that are used to control these conditions.

Management of the comorbid condition or removal of the offending toxin, e.g. alcohol or steroids, may improve the immune response of these patients. The likelihood of cannabinoid use influencing the human immune system either negatively or positively, is currently unknown. If these agents are indicated for the palliation of symptoms, it

seems reasonable to continue to monitor CD4 response as per the usual intervals recommended in current ART guidelines.

4.2 Morbidity and Mortality Risk from HIV Infection: General Indicators

While *all* should be able to access the costlier components of a palliative care service, e.g. admission to hospice and home nursing, it is acknowledged that the capacity of palliative care services in SA is limited. Who are in greatest need? No randomised, controlled palliative care trial addresses this question directly. Nevertheless, several observational studies identify associations that provide some answers (see Appendix B), these indicators change and their significance may diminish or reverse with time on ART. The following baseline characteristics in a large South African observational study influenced mortality in the first year after starting ART: WHO stage, body mass index (BMI), haemoglobin level, CD4 cell count, HIV plasma viral load (VL) and symptoms. Yet, once on long term ART, only CD4 cell count, BMI, haemoglobin level and a suppressed VL retained survival significance.[26] Another observational study that included data from South, Central and West Africa, found that age, gender and baseline CD4 cell count continued to predict death at 6, 12, 24 months and beyond, while taking ART.[27] These factors indicate need and not futility, i.e. they are not intended to be used to deny access either to ART or palliative care.

4.3 Mortality Indicators: Assessment Tools

4.3.1 Karnofsky Score

Although scores of ≤50% are often used as a qualifier for hospice admission, scores of <60% are significant and should trigger consultation with the palliative care team.[28] However, given the potential for ART to reverse underlying disease in the HIV-infected – the Lazarus effect – the absolute score must be viewed with caution. The usefulness of the Karnofsky score as a measure of impending mortality in this group of patients has not been established (see Appendix C for additional details).

4.3.2 The Support and Palliative Care Tools (SPICT^{TM})

These tools are used in the United Kingdom and have been applied to patients with HIV and cancer.[29] The tool is not specific to HIV and does not consider the role of ART and the curative potential of the treatment in several life-threatening infections, e.g. sulfonamides in cerebral toxoplasmosis and *pneumocystis jiroveci* pneumonia (PJP), TB drugs in disseminated TB, antifungals in cryptococcal meningitis (CM), etc.

- **General Indicators:**
  - Increasing physical and/or mental regression/dependency
  - A low BMI viz. <18Kg/m^2 and/or 5-10% loss of body weight
  - Ongoing and troublesome symptoms
  - Plea for supportive and palliative care or the wish to die

Assessment: Two or more 'general' indicators = unmet supportive and palliative care needs = qualify for palliative care benefits

- **Clinical Indicators:**
  - Worsening frailty and cognitive/neurological, cardiovascular and/or respiratory status
  - Worsening of cancer
  - Onset of life-threatening end-organ failure

  Assessment: One or more 'clinical' indicators = unmet supportive and palliative care needs = qualify for palliative care benefits (see Appendix D for additional details).

4.3.3 The Veterans Aging Cohort Study (VACS) Index.30

This scoring system was developed in North America and Europe, focuses on the HIV-infected, and uses seven clinical/laboratory indices that assist with the long term, viz. 6-year, prediction of survival (death) following the start of ART. Although the data reflects the experience of high-income countries and examines the risk of death in patients *already* on ART, the database is large, the index has wide applicability and its predictive value is superior to individual and composite indices currently in use.[31, 32] Most of the indices used in this system, with the exception of baseline hepatitis C virus (HCV) serology, are routinely performed in the public sector in SA. Local HCV prevalence is low, viz. 3-5%, and the absence of this index in the calculation of the score is unlikely to influence the result (see Appendix E for additional details).

4.3.4 Choosing an Assessment Tool for South African Patients

"Any attempt at prognostication that does not address whether the patient has had an adequate trial of ART would be ill-informed and inaccurate." (Merlin J, et al) [33]

In the United States (US), an estimated life expectancy of ≤ 6 months is sufficient reason to access hospice support,[33] though no similar timeline has been formally adopted in SA. While the VACS index has definite merit, it was not intended to answer the question of eligibility to specialised hospice benefits viz. home care and hospice admission. The SPICT tool has wide applicability but fails to take in the reversal of clinical disease on ART. This committee recommends the use of the SPICT tool where ART is unlikely to improve outcome, e.g. end-stage cancer, irreversible end-organ failure or where current or future ART is judged by the medical/palliative care team to be futile. With regard to patients in SA's private sector, provision of palliative care/hospice benefits is addressed in and supported by the South African Medical Schemes Act 131 of 1998.[34, 35] At this time, it is recommended that Medical Schemes utilise the SPICT tool when considering the reward of hospice benefits and/or the ≤6 month estimated survival time as practiced in the US. However, the patient must be on ART or switch to active ART if treatment failure has been confirmed and where ART remains a therapeutic option. Every HIV-infected person should be given the opportunity to access ART and enjoy its benefits. Where a patient refuses to take ART, yet requires hospice admission, addressing the patient's immediate need is of primary importance and the question of starting ART can be postponed.

5. MANAGING THE HIV-SICK: SYMPTOM CONTROL

5.1 Pain Control (See Appendix F (i-iii))

"Of all treatment modalities reviewed, the best evidence for pain reduction averages roughly 30% in about half of treated patients, and these pain reductions do not always occur with concurrent improvement in function. These results suggest that none of the most commonly prescribed treatment regimens are, by themselves, sufficient to eliminate pain and have a major effect on physical and emotional function in most patients with chronic pain." (Turck DC, et al) [36]

Chronic pain, i.e. pain lasting ≥3 months, is common in the HIV-infected and is often the reason for a palliative care consultation.[31] Pain in HIV-infected South Africans is likely to accompany an identifiable clinical cause and the most valuable contribution the HIV and palliative care physician can make to pain management is to identify the cause and treat it. The severity of the pain must be documented: Ask the patient to describe the pain and to rate it on a scale of 0 = "no pain" to 10 = "the worst pain I have ever experienced". Can the pain be fitted into a recognisable pattern, e.g. peripheral neuropathy, post-herpetic neuralgia, meningeal irritation, or is it associated with a specific site or organ, e.g. perianal ulcers/bedsores, pulmonary or pleural disease, a tumour such as Kaposi's sarcoma or a collection of enlarged lymph nodes? While the clinical examination will provide some answers, a pain assessment chart will ensure that no aspect of the pain is omitted (see Table 2).

The control of pain is a priority and must be addressed as soon as the patient arrives at a clinic or the admission ward. Tests to confirm the diagnosis are important but must not be allowed to delay the treatment of the pain, which works best when given by an interdisciplinary team.[36] Ideally, the team should offer, in addition to good medical and nursing care, most or all of the following:

- Physical rehabilitation
- Exercise therapy
- Cognitive restructuring that emphasises self-management, self-efficacy, and resourcefulness, i.e. activity rather than passivity, reactivity, dependency and hopelessness
- Behavioural treatment, e.g. relaxation and/or engagement in activities that enhance functionality
- Vocational rehabilitation if long term survival is not in doubt
- Drug management; in particular, the avoidance or reduction of opioid dependency
  N.B. Evidence-based support for opioids as improvers of chronic pain and functionality is weak, therefore their use must be weighed against their risks, e.g. addiction, hypogonadism, falls and fractures, depression, overdose and death.[36]

It is common to treat pain in a stepwise manner, starting with non-opioid medication such as paracetamol (acetaminophen), aspirin and the nonsteroidal anti-inflammatory drugs (NSAIDs) and ending with the opioids or combinations of opioids and non-opioids[37, 38] (see Table 3).

The 2017 Chronic Pain Guideline of the HIV Medicine Association of the Infectious Diseases Society of America (IDSA) provides an evidence-based evaluation of pain and its management in the HIV-infected.[39] In this assessment, only the following aspects of pain care received unanimous – "strong quality, high level" - support:

- Any 'new pain' in a patient with previously controlled pain needs fresh re-assessment
- Acetaminophen and NSAIDs are the first-line agents for the treatment of musculoskeletal pain in persons living with HIV
- Topical capsaicin is indicated for chronic HIV-associated peripheral neuropathy in conjunction with additional analgesics and supportive therapies and adequate viral control
- Screen all with chronic pain syndromes for depression, i.e. direct questioning, via a depression questionnaire and/or through a psychiatric referral.

Additional remarks that scored well viz. for their strong quality of evidence but did not secure unanimous support from reviewers included:

- The re-evaluation of pain among those with a 'changing experience of pain'
- The 'immediate/early' commencement of ART in those with a sensory polyneuropathy believed to be caused by HIV infection
- **Gabapentin,** with dose escalation up to a maximum of 2400mg daily po in divided doses, is recommended as the first-line oral treatment of chronic HIV-associated neuropathic pain (the authors note that somnolence occurs in 80% and can be problematic). The serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants and pregabalin received only weak or moderate support.
- Despite the absence of RCTs in HIV-related pain syndromes, **Alpha-lipoic acid (ALA)** received support for neuropathic pain treatment in view of its confirmed role in diabetic neuropathy, a condition that also targets the peripheral nerves.
- **Opioid analgesics** are not indicated for first-line control of neuropathic pain or chronic pain syndromes. Tramadol, a combination opioid, i.e. a serotonin + noradrenaline reuptake inhibitor + a μ-opioid agonist, received support, however, for use in several non-cancer pain syndromes including osteoarthritis, fibromyalgia and the neuropathic pain syndromes.[36]

5.1.1 Opioid therapy

Opioid therapy is often the treatment of choice for patients with cancer and those with moderate to severe pain.[38, 39] Although the WHO analgesic ladder recommends different opioids for different levels of pain, e.g. codeine for moderate pain and morphine for severe pain, cautious dose escalation using the initial opioid may avoid an unnecessary switch.[38, 40] Morphine can be given by several routes and subcutaneous, intramuscular and intravenous injection should be considered for those unable to swallow. Fentanyl is given by injection and transdermal skin patch but is not widely available to public sector patients in South Africa. Unwelcome respiratory complications can be avoided with the careful monitoring of opioid dose increases, which is particularly important where patients and families have expressed a desire for a pain-free yet lucid end to life.

Drug-drug interactions are important to note. Many drugs used in pain control viz. opioids, benzodiazepines, antidepressants and sedatives are substrates of the cytochrome P450 (CYP450) family of enzymes. Strong inducers or inhibitors of CYP450 will reduce (inducers) or potentiate (inhibitors) serum levels (efficacy/toxicity) of these drugs. Several antiretrovirals (ARVs) – especially the non-nucleoside reverse transcriptase inhibitors (NNRTIs - usually inducers), protease inhibitors (PIs - inhibitors) and drugs commonly used in the management of the HIV-sick e.g. rifampicin (inducer) for TB, carbamazepine and phenytoin sodium (inducers) for seizures, will influence the activity of substrates of this enzyme pathway (see Appendix F (i-iii)).

The nonmedical use of prescription opioids, which has become a major public health issue in the US and Europe[41], should not be withheld from people in need in low- and middle-income countries (LMICs), e.g. Africa and Asia. The authors of a recent Lancet Commission on Palliative Care and Pain Relief provide data to show that this does happen: "The fact that access to such an inexpensive, essential and effective intervention – opioid use for pain relief – is denied to most patients in LMICs and in particular to poor people – including many poor or otherwise vulnerable people in high-income countries – is a medical, public health and moral failing and a travesty of justice."[42] The Commission notes that the ten health conditions that result in the largest numbers of patients seeking palliative care in LMICs viz. malignancy, cerebrovascular disease, lung disease, injuries, TB, premature birth, trauma, HIV, liver disease, non-ischemic heart disease and dementia also account for about 95% of days of serious health-related suffering reported in these countries.

Table 2. The Pain Assessment Chart: Key Objectives[36]

Objectives in the Assessment of Severe Pain

1. **Characterise the multiple dimensions of the pain:**
   - Intensity
   - Temporal features: Onset, course, daily fluctuation and breakthrough pain
   - Location and radiation
   - Quality
   - Provocative or relieving factors
2. **Formulate an understanding of the nature of the pain:**
   - Cause
   - Probable pathophysiology
   - The Pain Syndrome: Neuropathy, cancer pain, post-herpetic neuralgia, etc.
3. **Characterise the effect of the pain on quality-of-life domains:**
   - Effect on physical function and wellbeing
   - Effect on mood, coping and related aspects of psychological wellbeing
   - Effect on role functioning and social/ familial relationships
   - Effect on sleep, mood, vitality and sexual function

4. **Clarify the extent of concurrent disease and review the planned treatment and prognosis.**

5. **Clarify the nature and quality of previous laboratory tests and previous treatments.**

6. **Review the HIV and ART history:**
    - Approximate duration of HIV infection and manner of confirmation
    - Counselling and Disclosure
    - Most recent CD4 count and viral load, plus all available lab results, including: FBC, U&E, LFTs and HBV/HCV status
    - ART exposure, adherence and viral failure/drug resistance
    - Prior opportunistic infections, e.g. TB, PJP, CCM and malignancies
    - Current symptoms in addition to pain

7. **Elucidate medical comorbidities.**

8. **Elucidate psychiatric comorbidities:**
    - Substance-use history
    - Depression and anxiety disorders
    - Personality disorders

9. **Identify additional needs that require palliative care interventions:**
    - Additional symptoms
    - Vulnerable /at-risk populations: Children, specific sexual identity groups, e.g. sex workers, injection drug users, migrants, refugees
    - Distress related to psychological or spiritual concerns
    - Caregiver burden and concrete needs
    - Problems in communication, care coordination and goal setting

Table 3. Guidelines for the Management of Acute Pain at the End-of-Life[38]

Type of Pain and Treatment	Initial Dosage	Comment
Mild-to-Moderate Pain		
Acetaminophen (Paracetamol)	1000mg orally or rectally 3-4 times a day	**Do not exceed 4g per day**. Use with caution in the presence of liver disease particularly in the elderly and with concomitant alcohol use.
Ibuprofen [NSAIDS]	800mg orally 3-4 times a day	GIT upset and bleeds, ulceration; Avoid in renal failure and use with caution in the presence of liver disease
Codeine	30mg with/ without 325mg acetaminophen orally every 3-4h as needed	**Do not exceed 360mg per day**. Note that constipation is usual. Provide advice regarding diet, exercise and the use of laxatives. Codeine can be addictive - use under supervision.
Oxycodone	5mg with or without 325mg acetaminophen, orally every 3-4h as needed	**If analgesia is inadequate** with initial treatment, adjust the dosage to 10mg orally every 3-4h as needed. As it can be addictive, use under s supervision.

Moderate-to-Severe Pain in Patients NOT Already on Opioids		
Morphine	Oral: 2-4mg every 30-60 min as needed IV: 2-5mg every 15-30 min as needed	For both morphine and hydromorphone, **if analgesia is inadequate with initial treatment,** increase the bolus dose by 25-50% for moderate pain or by 50-100% for severe pain. Morphine can be addictive, use under supervision.
Hydromorphone	Oral: 2-4mg every 30 min as needed IV: 0.4-0.8mg every 15-30 min as required	**If the level of analgesia is acceptable**, administer continuous infusion (equal to the total daily opioid dose) over 24h, with a breakthrough dose every hour equivalent to 10-20% of the total 24h opioid dose. **If the current drug causes unacceptable side-effects,** administer an equianalgesic dose of a different opioid. Addictive: Use under supervision.
Moderate-to-Severe Pain in Patients ALREADY on Opioids		
	Bolus dose, up to 10-20% of total opioid taken in the previous 24h, every 15-60min as needed	**If previously satisfactory analgesia** becomes inadequate, increase the basal and bolus dose by 25-50% for moderate pain or by 50-100% for severe pain. **For daily follow-up**, calculate the total 24h dose received viz. basal + breakthrough, and adjust the basal rate to equal this 24h opioid amount; Adjust the bolus dose to 10-20% of this 24h-total. If the current drug causes unacceptable side-effects, administer an equianalgesic dose of a different opioid.
Neuropathic Pain		
Opioids	Adjust dose until analgesia has been achieved	
Glucocorticoids	e.g. 4-16mg dexamethasone IV daily	Consider especially for acute neurologic injury such as nerve or spinal cord compression from a tumour.
Transdermal lidocaine patches	Consider especially when allodynia is present	
Short-acting antiepileptic drug, e.g. gabapentin, pregabalin or tricyclic antidepressant	If survival of more than a few days is anticipated, consider adding one of these agents immediately	

5.2 Fatigue, Weakness, Anorexia and Wasting (See Appendix F (i-iii))

Increased resting energy expenditure (REE) is a persistent accompaniment of HIV infection despite the use of ART.[43] In situations of inadequate food intake and altered food metabolism, weight loss may become severe. With every 1% increase in unintentional weight loss from the baseline measurement, there is a detectable increase in the risk of death of the HIV-infected patient.[44] The lower the BMI, i.e. below the normal value (BMI18-20kg/m^2), the greater the risk.[45]

Associations include:

- Disease of the mouth and upper gastrointestinal tract (GIT), e.g. **oesophageal candidiasis** and **cytomegalovirus (CMV)** infection and ulceration
- Anorexia. Consider medication, tumour and occult infection, e.g. **TB** (drug-resistant TB) or MAC. Drugs: **Chemotherapy, lopinavir/ritonavir**.
- Food insecurity. Particularly among refugees, migrants and the poor.
- Malabsorption, e.g. chronic diarrhoea, **GIT-TB or MAC**, tumour of the GIT. Send repeated stool samples (X 3) for parasites: **Cryptosporidia, cystoisospora spp**. Poorly controlled HIV infection = HIV enteropathy.
- Infection, particularly **end-stage HIV, TB, MAC** and **CCM**
- Disseminated **tumour**
- Hormonal deficiencies, e.g. Addison's disease, hypothyroidism and hypogonadism

♣ **Bold:** Frequent among the HIV-infected

Management: The HIV clinician will look for treatable causes but as the patient approaches death, symptomatic treatment will take priority. Start **ART** if treatment naive or check for resistance if on ART and the VL is detectable. **Glucocorticoids**, e.g. dexamethasone 2-4mg daily po or IV, can be considered at the end of life as the risk of additional immunosuppression is unlikely to influence the outcome. Steroids are often given to stimulate the appetite and/or to counter the fatigue and weakness of the final illness. Vigilance is indicated if steroids are given for a prolonged period and patients should be monitored for: hypertension, hyperglycaemia, gastrointestinal bleeds, fluid retention, proximal myopathy, confusion and psychosis. **Testosterone** has benefited hypogonadal individuals with fatigue[46] and the stimulants, **modafinil** and **armodafinil,** have had success in reducing fatigue in small RCTs, but caution is advised in view of limited data and the risk of drug abuse.[31] Invasive procedures, such as nasogastric feeding and percutaneous endoscopic gastrostomy, are discouraged at the end of life but may be considered where a reversible condition has been identified. Ensure good nursing, keep the oral mucosa clean, moist and wet and mobilise the indigent patient where possible. Avoid bedsores and treat oral thrush with **topical nystatin drops** 2-5ml "swish and swallow" 5X a day or **oral fluconazole** 50-100mg daily until the infection clears. If oesophageal candida is diagnosed, give oral fluconazole 100-200mg daily X 7-10 days. A short course of **IV amphotericin B** can be considered if unable to swallow the fluconazole. Treat oral and oesophageal herpes simplex aggressively, prescribe **oral acyclovir** (public sector) or **valaciclovir** (private) if the infection is mild and confined to the mouth and IV acyclovir for disease that is extensive, virulent or involving the oesophagus. Continue treatment *until* the infection has cleared viz. usually 7-10 days and control the pain which often requires strong analgesia, e.g. codeine or tramadol. Food should be liquidised or very soft, to minimise oral pain while the infection is acute.

5.3 Dyspnoea and Cough (See Appendix F (i-iii))

The anatomy of the cough reflex incorporates the upper and lower airways and the afferent and efferent neural connections to and from the cough centres within the brain.[46] Disease at any of these sites may be responsible for cough, however, in the

HIV-infected, cough usually directs attention to the lung. An acute cough lasts days to a few weeks and a chronic cough lasts for ≥8 weeks.[47]

What follows includes:

- **Bacterial pneumonia**: Productive cough, fever, chest pain, sudden onset, acute history. Aspiration pneumonia is frequent at the end of life.
- **Pulmonary TB** (PTB): Productive cough, haemoptysis, chest pain, fever, night sweats, weight loss, chronic history or past history of TB, TB contact history.
- **PJP**: A dry incidental chronic cough, worsening dyspnoea with effort, later dyspnoea at rest, severe hypoxia at rest, worsens with exertion/effort, little or no fever, minimal chest pain, profound fatigue/exhaustion, tachycardia and unrelenting tachypnoea. Often a bedside diagnosis!
    - **PJP**: **Poor prognosis**. The persistence of hypoxia/respiratory failure, tachypnoea and tachycardia despite treatment, no decrease in baseline LDH level with treatment, worsening of the chest X-ray (CXR) on treatment, elevated APACHE II score.[48, 49]
    - **PJP: Prevention**. Initiation onto ART soon after the initial infection with HIV and prophylactic use of trimethoprim-sulfamethoxazole with all baseline CD4 cell counts <350 cells/mm^3 are recommended.[50, 51]
    - **PJP: Ethics.** The decision to admit to ICU and to ventilate usually rests with the ICU clinician/ resident pulmonologist, however, this action may be futile, i.e. does not guarantee success/survival. The palliative care team must make itself familiar with this scenario in order to provide wise support (insight and understanding) to patients and colleagues and where possible, the death of a patient in the ICU and on a ventilator should be avoided. This is a source of great suffering for patients and their loved ones, though is best managed through discussion with the patient, family and friends *before* the urgent need of ICU admission and ventilation arises.

Causes of dyspnoea/cough include: [47]

- **Acute infection:** Trachea-bronchitis, **pneumonia** (viral and bacterial)
- **Chronic infection**: Bronchiectasis, chronic lung infection (bacterial, e.g. **TB**, **MAC**, lung abscess), fungi (***PJP*, cryptococci**, histoplasmosis), protozoa (toxoplasmosis) and rarely helminths
- Airway diseases: Asthma, chronic bronchitis, postnasal drip
- Disease of the parenchyma and vessels of the lung: Chronic interstitial lung disease, emphysema, sarcoidosis, pulmonary vascular disease viz. embolic, vasculitis, pulmonary hypertension
- **Tumour**: Primary or secondary (metastases to the lung)
- Cardiovascular disease: Left ventricular failure, right-sided endocarditis
- **Anaemia**: Severe dyspnoea, Hb <8g/dl
- GIT: Acid reflux, aspiration pneumonia (cough often at night)
- Metabolic acidosis: Diabetic ketoacidosis, **lactic acidosis (NRTIs: zidovudine, stavudine), renal tubular acidosis (tenofovir disoproxil fumarate):** Tachypnoea and dyspnoea but with normal oxygenation ($p0_2$), chest auscultation normal, CXR clear
- Drugs: Angiotensin-converting enzyme (ACE) inhibitors (cough)

- ♣ **Bold:** Frequent among the HIV-infected

Management: Many of the conditions that present with cough and dyspnoea in the HIV-infected patient are treatable. However, some, such as non-responsive PJP or end-stage (destroyed) lung disease whether from previous TB or from COPD, may not be reversible and will require palliation. Blood gas measurements, blood transfusion, intubation and ventilation are likely to be inappropriate when death is imminent. Supportive care such as oxygen, bronchodilators, steroids and antimicrobials may be prescribed if indicated and diuretics may be needed to treat pulmonary oedema/fluid overload. **Opioids** are regarded as the treatment of choice for dyspnoea in the context of end-of-life care. These can be given safely, i.e. without the risk of respiratory depression, if titrated carefully with attention to dose and response.[38] In addition, the careful use of **benzodiazepines** may relieve anxiety associated with breathlessness and asphyxiation.[38]

Specific end-of-life therapies include the following:
- **Morphine:** 5-10mg po every 30 min as needed until the patient is comfortable, or IV 2-4mg every 30 min to 1h as needed until the patient is comfortable.
- **Oxygen**: Adjust to achieve satisfactory saturation and subjective relief of dyspnoea.
- **Non-pharmacologic measures**: Support, relaxation and breathing exercises, etc.

5.4 Dry Mouth/Xerostomia

Causes of dry mouth/xerostomia include:
- Poor oral immunity: Often a sign of advanced HIV/AIDS with/without HIV-associated dementia (HAD); Poorly controlled diabetes mellitus, gingivitis
- Infection: Chronic parotitis, salivary duct obstruction (stones, tumour), extensive **oral candidiasis**
- Autoimmune: Sjögrens syndrome
- Drugs: Anticholinergics, alpha- and beta-blockers, diuretics, calcium channel blockers
- Post-irradiation, e.g. cancer of the head and neck

- ♣ **Bold:** Frequent among the HIV-infected

Management: Address the cause, clean the mouth regularly, maintain hydration - oral fluids if able to swallow, chewing gum/mildly acidic sweets (lemon drops), stop offending drugs (above), artificial saliva.

5.5 Nausea and Vomiting

Nausea is defined as the subjective feeling associated with the action of vomiting. Identify and treat the cause, including the common associations below:

- Abdominal conditions: **Gastroenteritis**, intestinal diseases (inflammatory, obstructive)
- General causes: Middle ear and **CNS disease,** e.g. **meningitis and raised intracranial pressure (RICP)**; Anxiety and fear; Cardiac, e.g. acute myocardial infarction; Endocrine, e.g. pregnancy, diabetic ketoacidosis; Pancreatitis; End-organ failure, e.g. renal **(uraemia), liver disease**, adrenal
- Drugs: **ARVs, e.g. zidovudine, lopinavir/ritonavir**; Antimicrobials, e.g. macrolides, beta-lactams, **TB drugs**; Chemotherapy (oncology); Digoxin; Opioids; Alcohol-intoxication, etc.

    ♣ **Bold:** Frequent among the HIV-infected

Management: Address the cause. Inner-ear or motion sickness require antihistamines, e.g. dimenhydrinate, cyclizine; If drug-related - antidopaminergic, e.g. prochlorperazine; If chemotherapy-related - 5-HT_3 antagonist, e.g. ondansetron, granisetron; If intestinal and gastro-related - 5-TH_4 agonist, e.g. cisapride, metoclopramide, and somatostatin analogues, e.g. octreotide. Chemotherapy-induced leads to anticipatory nausea and vomiting/ CNS arousal syndrome, and anxiety should be addressed with a benzodiazepine, e.g. lorazepam, glucocorticoids, e.g. methylprednisone, dexamethasone or with cannabinoids, e.g. tetrahydrocannabinol (see Section 7 below).

Suggested end-of-life treatment:

- **Bowel obstruction**: Octreotide 100-200µg subcutaneous injection 3 times a day or 100-600µg per day in an IV infusion. Should a nasogastric tube (NGT) be placed? Where the likelihood is that this will provide little/no improvement and where the expectation that death is within hours or a few days, it is more humane to withhold NGT and maximise alternative forms of symptomatic relief.
    - Dexamethasone 4-8mg po/IV daily: Maximum 16mg daily.
- **Gastroparesis:**
    - Metoclopramide 10-20mg po/IV every 4-6 h: Maximum 100mg per day.
- **Elevated intracranial pressure**:
    - Dexamethasone 4-8mg po/IV daily: Maximum 16mg daily.
- **Unspecified cause but including chemotherapy**:
    - Metoclopramide 10-20mg po/IV every 4-6 h: Maximum 100mg per day.
    - Haloperidol Oral: 1.5-5mg 2-3X per day IV: 0.5-2mg every 8h.
    - Ondansetron 8mg po 8h as needed.
    - Dexamethasone 4-8mg po/IV daily: Maximum 16mg daily. Usually combined with other anti-emetics.[52, 53]

5.6. Constipation

Infrequent emptying of bowel/rectum often with a sensation of incomplete evacuation. Seldom secondary to a significant medical problem.

- **Acute/recent onset**: Local problem viz. tumour, stricture, trauma or **analgesics including opioids; Inactivity;** Not eating.
- **Chronic:** Irritable bowel syndrome; Hypothyroidism; Hypercalcemia; Pregnancy; Chronic CNS disorders, e.g. Parkinson's disease, paraplegia etc.; Drugs, e.g. antidepressants, calcium channel blockers, **analgesics, including opioids**.

- ♣ **Bold:** Frequent among the HIV-infected

Management: Treat the cause. Where feasible, encourage the patient to mobilise and take in more fluids and increase dietary fibre (bran) including vegetables and fruit. The following medicines can be tried, e.g. lactulose, psyllium, bisacodyl and fleet enemas, as management must be expectant and preventive.

Suggested end-of-life care:

- Senna 2-4 tabs (8.6mg sennosides per tab) or 1-2 tabs as a single daily dose or in two divided doses per day. Do not exceed 100mg per day.
- Bisacodyl suppository: 10mg given rectally per day as needed.

5.7 Fever

Fever in someone with HIV infection usually suggests an infectious complication. The constellation of fever, cough, weight loss and night sweats in an HIV-infected person in Africa indicates a heightened suspicion of tuberculosis, however TB must be confirmed as it is a treatable, transmissible disease and its presence puts others at risk. Even at the end of life, TB must be diagnosed, treated and controlled and it is particularly important to check whether the disease is drug-resistant or not (Gene Xpert analysis gives information about rifampicin sensitivity or resistance). Even in the context of palliative care, patient isolation and infection control measures must be implemented.

If fever is part of an end-of-life infection, such as an aspiration pneumonia, the patient and their family may resist the idea of prolonging the inevitable with antibiotics and active interventions. The task of the palliative care team is to assist the patient to face the inevitability of death yet at the same time, the team must agree to do all that it can to minimise suffering, i.e. to support the patient. This is where the palliative care physician and team provide what is frequently missing from the wards of our South African hospitals as death should be about healing even when the latter is not delivered by way of pills, lines and procedures.

Management: Treat the cause when a fever is indicated. Paracetamol, aspirin, NSAIDS and sometimes steroids may assist in controlling it while tepid sponging, a fan and oral fluids may help to alleviate the patient's distress. Avoid paracetamol in patients with liver disease. Antimicrobial therapy that is not directed at a particular pathogen or a likely diagnosis is unlikely to be helpful at the end-of-life. Prophylactic trimethoprim-sulfamethoxazole is recommended if the baseline CD4 count is <350c/mm^3 and/or an AIDS-defining illness (or WHO Stage 3 and 4 disease) is present.[50]

Suggested end-of-life care:

- Paracetamol/acetaminophen 650-100mg po/pr or IV every 4-6h as needed: maximum daily dose=4g.
- Naproxen 250-500mg po bid (Short course x 2-3 days. Can be repeated.)

5.8 Confusion, Neurological Disease in the HIV-Infected

HIV infects the human brain. This occurs during the first few weeks following acquisition of the virus and establishes a chronic but usually low-grade infection which persists for the remainder of the individual's life. Neurological consequences are frequent but are generally mild or asymptomatic[54], though antiretroviral therapy helps to control this central nervous system (CNS) infection. If ART has not been taken, or if the virus in the CNS has become resistant to this therapy, the function of the brain will be impaired, e.g. HIV encephalopathy. The latter is a life-threatening and dementing process characterised by motor-slowing, abnormal movement (basal ganglia involvement) and progressive cognitive decline. HIV also attacks the peripheral nervous system (PNS) and is responsible for a painful symmetric sensory polyneuropathy that leaves the individual wheelchair/bedbound and in constant pain.

Several of the following conditions need to be considered in the HIV-infected patient with serious neurological disease[54], as detailed in Table 4 below:

Table 4. HIV+ Concurrent Disease and Commentary

Disease	Commentary
Cerebrovascular disease: Cerebrovascular accident	Comorbid disease, e.g. hypertension, diabetes mellitus, renal disease, cardiovascular disease. **Hyperlipidaemia with AZT, ddI, d4T and the PIs**
Depression	May present with dementia, psychosis
Intoxication/medication	**Toxicology screen**: Alcohol and recreational drugs, though consider **efavirenz (EFV) encephalopathy** and **isoniazid toxicity.** Steroid psychosis.
Progressive multifocal leukoencephalopathy (PML)	MRI = white matter lesions. IRIS following ART initiation = gadolinium enhancement on MRI
Metabolic encephalopathy	Vit. B12/ folate deficiency, end-organ failure, antimicrobial encephalopathy, e.g. metronidazole
Syphilis	Check the blood and CSF syphilis serological tests: VDRL, TPHA
Toxoplasma encephalitis	CT/MRI brain scan: Contrast (ring) enhancing lesions; Antibody test positive in serum and CSF
HIV encephalitis: Untreated infection	CT/MRI: Loss of brain volume, prominent sulci, dilated ventricles, high CSF viral load. NB. Increased cells (lymphocytes) and marginally raised total CSF protein, with a normal glucose and negative tests for specific pathogens may be pointing to HIV itself as the cause of the encephalopathy.
HIV encephalitis: Viral Escape or Compartmentalisation Syndrome[55]	CT/MRI as above. **HIV viral load in CSF** higher than serum viral load. CSF = active (cells, raised protein)
CMV encephalitis	PCR (viral load) and pp65 antigen in CSF, CMV retinitis and/or ulceration of the gastrointestinal tract (mouth to anus) make indicate 'active' CMV.
Bacterial meningitis, e.g. **TB meningitis (TBM)** [56, 57]	CSF = high protein, low sugar, cells (lymphocytes), TB found elsewhere, e.g. LAM test (Urine) or gene XPert positive on sputum or CSF; TB culture (blood).

Fungal meningitis, e.g. **Cryptococcal meningitis (CCM)** [58, 59]	CSF = high protein, low sugar, cells, CrAg or CLAT positive yeasts seen, crypto culture on CSF positive.
Herpes simplex/varicella encephalitis	CT/MRI: Focal infarct or bleed, vasculitis on Magnetic Resonance Imaging and Angiography (MRA) to confirm a vasculitis, PCR (viral load) on CSF. **Active Shingles** on the face, e.g. Ophthalmic division of the Trigeminal nerve, the Ramsay Hunt Syndrome.

Management: Treat the cause where identified. Is the patient on ART (efavirenz)? TB drugs (Isoniazid)? Is the HIV infection controlled in the serum and in the CSF?

Suggested end-of-life care:

- Lorazepam for anxiety: 0.25-2mg po or IV or S/C every 4-6 h as needed. Increase dose to 5mg if necessary.
- Haloperidol for delirium: 0.5-1mg po or IV every hour as needed. When symptoms have settled, give the daily total dose in 3-4 divided doses through the day.

6. HIV, CANCER AND PALLIATIVE CARE IN SOUTHERN AFRICA

Cancer case fatality rates are higher in low-income regions such as Africa (75%) than in high-income regions viz. Europe and North America (46%).[60] On the back of this, the growing numbers of HIV-infected persons with cancer, a so-called 'hidden cancer epidemic' in LMICs, is of concern.[61-62] More than a decade ago, SA researchers recorded the prevalence of several cancers among HIV-infected South Africans[63] (see Table 5 below). Odds ratios confirmed a substantial increase in risk among the HIV-infected, particularly for the traditional AIDS-defining tumours and in Africa, these cancers still predominate: Kaposi's sarcoma, non-Hodgkin lymphoma, cervical carcinoma and CNS lymphoma. The incidence of non-AIDS-defining cancers, however, in the region, e.g. Hodgkin's disease, solid tumours of the lung, GIT and breast, etc., is rising despite the use of ART. The latter is a global trend and affects HIV-infected people who are younger than the HIV-negatives in the community with the same tumours.[64, 65]

Table 5. The Association of Certain Cancers with HIV-1 Infection in South Africa, 1995-2004 [63]

Cancer site or type	Total (N)	HIV-1 + (%)	Odds Ratio, (OR, 95% CI, adjusted for age, sex and year of diagnosis)
Kaposi's sarcoma	333	89.2	50.4 (34.2-74.3)
Non-Hodgkin's lymphoma	223	44.4	6.1 (4.4-8.4)
Squamous cell, skin	70	21.4	2.6 (1.4-4.7)
Anogenital other than cervix	157	22.3	2.5 (1.7-3.8)
Cervix	1,586	14.9	1.7 (1.4-2.0)
Melanoma	53	15.1	1.6 (0.7-3.5)
Hodgkin's lymphoma	154	19.5	1.5 (1.9-2.4)

Legend. This table provides odds ratios that define the occurrence of various cancers in HIV-infected South Africans during the time period 1995-2004. All of the cancers represented were

associated with HIV infection rates greater than that of HIV itself in the general South African population of the time.

Establishing early linkage to care, particularly to palliative and HIV care, is essential if the goal of improved survival and the relief of suffering is to be reached. However, several hurdles must be overcome:

- **Late presentation**. Stigma, misunderstanding and denialism continue to stand in the way of early detection of HIV and cancer. Patients present at an advanced HIV stage, naïve to ART, with a low baseline CD4 level and multiple competing diagnoses.

- **Delays in receiving cancer treatment.** Large patient numbers, few or inadequately skilled staff, insufficient specialists and unsupportive management cause delayed treatment. In many instances, patients die before test results return and before a link with oncology/radiotherapy is made. Thirty African and Asian countries have no radiotherapy machines and in many LMICs, oncologists, if present, are restricted to the largest cities.[66]

- **Laboratory support.** Obtaining reports, e.g. biopsy (histology) results, in the public sector in SA is plagued by long delays, while histology reports in the private sector return within a couple of days, and oncology referrals in the public sector cannot be processed without the confirmatory histology. In the absence of histological confirmation, patients die while awaiting their test results or while awaiting their oncology appointment.

- **HIV and cancer therapy.** Chemotherapy in Africa and SA's public sector is frequently characterised by the ongoing use of drugs no longer viewed as optimal in developed regions.[67] Problems include: post-chemotherapy neutropenia, HIV immunosuppression, antimicrobial resistance, frequent drug stock-outs and drug-drug interactions between cytochrome P450 substrates, inducers and inhibitors and ARVs.

How can the HIV-infected cancer patient be better served?

- **Prevention**
  - Tobacco use control
  - Hepatitis B vaccination
  - Hepatitis C serology and access to directly-acting antivirals (DAAs)
  - Human papillomavirus (HPV) vaccination
  - Cervical and anal Pap smears
  - **The early introduction of ART.** Uncontrolled plasma (HIV) viral load is associated with the increased risk of malignancy in the HIV-infected.[68, 69]

- **Baseline determination of HIV status of every cancer patient.** Survival of the HIV/cancer patient requires access to ART and long-term suppression of HIV.[70, 71]

- **Linkage to care.** The ethos of this care is holistic, i.e. oncology, HIV-caregivers and the palliative care team work together in the support of the patient.

- **Collaboration is needed between Oncology/ Radiotherapy and the disciplines of HIV/Infectious Diseases and Palliative Care.** Cancer care in SA must be sensitive to the needs of the HIV-infected, and closer collaboration between HIV, palliative care physicians and oncology/radiotherapy specialists must take place if weak links in healthcare delivery are to be strengthened. ARV drugs and regimens are constantly changing, drug-drug interactions and toxicities are common, and secondary infection with opportunistic microbes frequently occur. A team approach is required to improve survival outcome in this group of patients.

7. THE CANNABINOID DRUGS IN THE PALLIATIVE MANAGEMENT OF HIV-INFECTED PATIENTS

South Africa's courts have recently legalised cannabis for medical use. Data in HIV-infected people is sparse and restricted to observational reports, and though the use of these compounds is widespread both in Africa and globally, the hostility to its use is slowly changing. Nonetheless, data is beginning to emerge.[72] An observational study in >3000 cancer patients noted cannabis improved sleep, anxiety and depression levels, and reduced the fatigue, nausea and vomiting of chemotherapy.[73] A report of 198 HIV-infected 'heavy' cannabis users noted reduced activation of inflammatory markers compared with non-cannabis using controls, however, there is clearly a need to better clarify the role of the cannabinoids in evidence-based, well planned randomised controlled trials of the HIV-infected and uninfected.[74] The 2016 Johns Hopkins-Lancet Commission on Drug Policy and Health makes the additional point: "At a time of policy-level concern about dependence on prescription opioids, a few ecological studies suggest that greater access to cannabis could reduce use of opioids for pain relief." [75]

Cannabinoid side-effects are common, usually dose-dependent, i.e. higher doses tend to produce more side-effects, and are often specific to individual compounds (see Table 6). These side-effects include, cardiac (tachycardia, hypo- and hypertension), CNS (arousal and depression states, e.g. cognitive impairment, euphoria, psychosis and paranoia), and with high doses, gastrointestinal toxicity viz. diarrhoea, vomiting and abnormal liver biochemistries (LFTs).[72]

With regard to the role of cannabinoids in the palliative care of HIV-infected patients, several 'unknowns' remain, e.g. [72]:

- Indications for use of cannabinoids require urgent clarification
- The pharmacokinetics and pharmacodynamics of cannabinoids in people naïve to and those with prior exposure (to cannabinoids) in the context of palliative care. Does this differ? Do the cannabinoid-exposed require a higher dosing of cannabis?
- Drug-drug interactions between the cannabinoids, ART and TB drugs have minimal/no data
- Which route of administration should be recommended: oral, inhaled (smoked)?

Table 6. Recommendations for Cannabinoid Use in Symptom Management of HIV/Palliative Care [72]

Symptoms and Recommended Medication	Evidence	Comment on Medication and Route of Administration
Nausea and Vomiting	Antiemetic effects when CB1 receptors activated by THC	THC-rich products: Inhaled
	Dronabinol: superior anti-emetic activity versus neuroleptics in cancer patients	
	Synergistic effect for **dronabinol** and prochlorperazine	
	Non-inferiority for **dronabinol** versus 5-HT3 antagonists	
	CBMs greater activity in suppressing anticipatory nausea in pre-clinical model	
Pain (i) Dronabinol	10mg better than 20mg	THC-rich products
	Mild analgesic effect comparable to 60mg codeine	THC/CBD 1:1
	Adverse reactions (20mg): dizziness, somnolence, ataxia, blurred vision	Inhaled: Breakthrough pain/ pain crises = immediate benefit.
Pain (ii) Nabiximols	Low dose (1-4 sprays/day), medium dose (6-10 sprays/day), high dose (11-16 sprays/day)	Oral: Persistent pain ("long-acting" effect)
	Analgesia with low and medium dose vs. placebo, poor drug tolerability with high dose	
Pain (iii) Natural Cannabinoids	Reduction in pain intensity, opioid-sparing potential, synergism effect with opioids	
Pain: Improvement in pain measures with the use of cannabinoids compared with placebo **Pain:** Benefit from the use of inhaled cannabis treatments for neuropathic pain **Pain:** Prevention of chemotherapy-induced neuropathy in pre-clinical studies		
Appetite stimulation	**Dronabinol: Increased appetite and weight stability in HIV/AIDS and dementia**	THC-rich products: I**nhaled or oral**
Appetite: Dronabinol versus megestrol acetate for cancer-associated anorexia: Findings in favour of megestrol **Appetite:** THC 2.5mg versus THC 2.5mg + CBD 1mg versus placebo: No significant improvements in survival, weight or other nutritional variables. **Appetite:** Increased weight with smoked cannabis in experienced HIV+ marijuana smokers **Appetite:** Improved taste, smell and food enjoyment using oral dronabinol		
Insomnia:	Positive association between cannabinoids and improved sleep quality	THC-rich products
	Lack of evidence in cancer/palliative care population	Inhaled: Sleep induction

		Oral: Sleep maintenance
Depression and Anxiety	**Nabiximols:** High doses have negative effect in depression, positive results for anxiety disorders	**Anxiety**: CBD-rich **Depression:** THC-rich or THC/CBD 1:1 Inhaled: Panic attacks or anxiety
	(ii) CBD-rich products recommended for patients with psychiatric disease	Oral: For persistent symptoms
	THC may exacerbate other conditions, e.g. schizophrenia, psychosis, and bipolar disorder	

8. FINAL REMARKS

Box 2. Thomas Brown, The Religio Medici[76]

> **"Men that look no further than their outsides, think health an appurtenance unto life and quarrel with their constitutions for being sick; But I that have examined the parts of man, and know upon what tender filaments that fabric hangs, do wonder that we are not always so; And considering the thousand doors that lead to death, do thank my God that we can die but once."**
>
> Thomas Browne, 1642. The Religio Medici.
>
> Quoted in Ferry G. Thomas Browne: A rarity among rarities. *Lancet* 2017; 389: 1687-88

It was the general belief in the 1980's that a vaccine and cure would have been found by the end of that decade or at the latest, the middle of the 1990s. That has not occurred, and the HIV epidemic is now firmly rooted in southern African soil. ART has transformed the infection into a chronic, manageable disorder yet the condition remains incurable. Close to 8 million HIV-infected South Africans need care and will die from or with the virus. Their suffering is the concern of these guidelines as many will require palliative care.

The 'total pain' that accompanies suffering arises from multiple causes. Analgesics alone do not effectively control this pain though palliative care teams throughout the country's health service would go a long way to answer this need. Even highly motivated teams require funding, organisation and the support of colleagues and government in a country where its public health is in trouble: Under-funded, overcrowded, ageing facilities in need of renewal and a department facing extraordinarily high levels of litigation.[77, 78]

Developing a discipline of palliative care and fitting it into this failing system and at this time will be a testing experience, but it must happen. Somehow.

The private sector must find a reliable tool that funders can use when providing capital for home nursing and hospice admission. A life-expectancy of 6 months or less is a widely-used rule of thumb in the US, though available models are generally insensitive to the gains of ART and the treatment of opportunistic disease. No local RCTs answer this question, nonetheless, our recommendation has been to follow the US approach and use the 6-month probability of survival or the SPICT^{TM} tool.

The defining treatment ethos of HIV and ID clinicians is curative. There is no conflict between curative and symptomatic management provided the goal to treat suffering is central to care. Is there a time where curative care is no longer appropriate? Is there a time to let go of ART? Yes. Those of us who are hospital-based clinicians encounter these questions daily in our busy wards yet know that the answers are not found in textbooks. They are found at the bedside.

REFERENCES

1. National Policy Framework and Strategy on Palliative Care, 2017-2022. South African Department of Health. Final Draft. 23 March 2017

2. World Health Organization (WHO) at http://www.who.int/cancer/palliative/ definition/en/ accessed on 19 November 2017.

3. Cassel EJ. The Nature of Suffering and the Goals of Medicine. Second Ed., pg 31. Oxford University Press., 2004

4. UNAIDS Data 2017. http://www.avert.org. Accessed 05.01.2018. HIV and AIDS in South Africa.

5. STATS SA. Data accessed via http://www.statssa.gov.za on 10.10.2017

6. DC Spencer. Personal communication with colleagues in the hospitals of Gauteng, Mpumalanga and the Free State. 03.02.2018

7. Welz T, Hosegood V, Jaffar S, et al. Continued very high prevalence of HIV infection in rural KwaZulu-Natal, South Africa: a population-based longitudinal study. AIDS 2007; 21 (11): 1467-72

8. Black A, Kriel J, Mitchley M, Williams B. The burden of HIV in a Public Hospital in Johannesburg, South Africa. (2015) arXiv:1412.2788. Available at https://arxiv.org/pdf/1512.04781.pdf).

9. Wong EB, Omar T, Setlhako GJ, et al. Causes of Death on Antiretroviral Therapy: A Post-Mortem Study from South Africa. *PLoS ONE* 2012;7(10): e47542 doi.10.1371/journal.pone.0047542

10. Van Rie A, Westreich D, Sanne I. Tuberculosis in Patients Receiving Antiretroviral Treatment. *J Acquir Immune Defic Syndr* 2011; 56(4): 349-55

11. Richards L. Unpublished data collected and tabulated for the Degree of M.Med (Internal Medicine) from the University of the Witwatersrand, Johannesburg. Submitted July 2018.

12. Lunney JR. et al. Patterns of Functional Decline at the End of Life. JAMA 2003; 289: 2387-92

13. Gawande A. Being Mortal. Cpt. 2 pg 25. Things Fall Apart. Wellcome Collection. 183 Eustace Rd., London. NW1 2BE. Published in 2014

14. Simms V, Higginson IJ, Harding R. Integration of palliative care throughout HIV disease. *Lancet Infect Dis* 2012; 12: 571-75

15. Jambo KC, Banda DH, Afran L, et al. Asymptomatic HIV-infected Individuals on Antiretroviral Therapy Exhibit Impaired Lung CD4+ T-Cell Responses to Mycobacteria. *Am J Resp Crit Care Med* 2014; 190(8): 938-947

16. Almodovar S. The Complexity of HIV Persistence and Pathogenesis in the Lung under Antiretroviral Therapy: Challenges Beyond AIDS. *Viral Immunology* 2014; 27(5): 186-190

17. Ferrand RA, Desai SR, Hopkins C, et al Chronic Lung Disease in Adolescents With Delayed Diagnosis of Vertically Acquired HIV Infection. *Clin Infect Dis* 2012; 55(1): 145-52

18. Desai SR, Nair A, Rylance J, et al. Human Immunodeficiency Virus-Associated Chronic Lung Disease in Children and Adolescents in Zimbabwe: Chest Radiographic and High-Resolution Computed Tomographic Findings. *Clin Infect Dis* 2018; 66(2): 274-81

19. Maddocks M, Lovell N, Booth S, Man W D-C, Higginson IJ. Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease. *Lancet* 2017; 390: 988-1002.

20. Drummond MB, Kirk GD. HIV-associated obstructive lung diseases: insights and implications for the clinician. *Lancet Respir Med* 2014; 2(7): 583-592 doi:10.1016/S2213-2600(14)70017-7

21. May MT, Gompels M, Delpech V, et al. Impact on life expectancy of HIV-1 positive individuals of $CD4^+$ cell count and viral load response to antiretroviral therapy. *AIDS (London, England)*. 2014; 28(8):1193-1202. doi:10.1097/QAD.0000000000000243.

22. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; 363: 733-42

23. Gazzola L, Tincati C, Bellistri GM, et AL. The Absence of CD4+ T Cell Count Recovery Despite Receipt of Virologically Suppressive Highly Active Antiretroviral Therapy: Clinical Risk, Immunological Gaps and Therapeutic Options. *Clin Infect Dis* 2009; 48: 328-3724.

24. Serrano-Villar S, Sainz T, Lee SA, et al. HIV-Infected Individuals with Low CD4/CD8 Ratio despite Effective Antiretroviral Therapy Exhibit Altered T Cell Subsets, Heightened CD8+ T Cell Activation and Increased Risk of Non-AIDS Morbidity and Mortality. *PLoS Pathog* 2014; 10(5): e1004078. Doi:10.1371/journal.ppat.1004078

25. Nanzigu S, Kiguba R, Kabanda JK, et al. Poor immunological recovery among severely immunosuppressed antiretroviral therapy-naïve Ugandans. *HIV-AIDS Research and Palliative Care* 2013; 5: 309-319

26. Hoffmann CJ, Fielding KL, Johston V, et al. Changing predictors of mortality over time from cART start: implications for care. *J Acquir Immune Defic Syndr* 2011; 58(3): 269-76

27. Yiannoutsos CT, Johnson LF, Boulle A, et al. for the International Epidemiologic Databases to Evaluate AIDS (IeDEA) Collaboration. Estimated mortality of adult HIV-infected patients starting treatment with combination antiretroviral therapy. *Sex Transm Infect* 2012; 88(suppl 2):i33-43. Doi: 10.1136/sextrans-2012-0506558

28. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The Use of the Nitrogen Mustards in the Palliative Treatment of Carcinoma – with Particular Reference to Bronchogenic Carcinoma. *Cancer.* 1948; 1(4):634-56

29. The Support and Palliative Care Indicator Tools (SPICT^{TM}). University of Edinburgh, SPICT^{TM}, April 2015, http://www.spict.org.uk.

30. Tate JP, Justice AC, Hughes MD, et al. The VACS Index: An internationally generalizable risk index for mortality after one year of antiretroviral therapy. AIDS 2013; 27(4): 563-572 doi:1-/1097/QAD.06013e32835b8c7f.

31. Justice AC, Modur S, Tate JP, et al. for the NA-ACCORD and VACS Project Teams. Predictive Accuracy of the Veterans Aging Cohort Study (VACS) Index for Mortality with HIV Infection: A North American Cross Cohort Analysis. *J Acquir Immune Defic Syndr.* 2013; 62(2): 149-163. Doi:10.1097/QAI.0b013e31827df36c

32. Gustafson DR, Shi Q, Holman S, et al. Predicting death over 8 years in a prospective cohort of HIV-infected women: the Women's Interagency HIV Study. *BMJ Open* 2017; 7: e013993. Doi.10.1136/bmjopen-2016-013993

33. Merlin J, Pahuja M, Selwyn PA. Palliative care: Issues in HIV/AIDS. Literature review current through to September 2017. Accessed online, February 20, 2018.

34. Prescribed Minimum Benefits, The Medical Schemes Act 131 of 1998 of the Republic of South Africa.

35. http://www.medicalschemes.com/files/Circulars/circular21of 2017.pdf. Published March 16, 2017

36. Turck DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. *Lancet* 2011; 377: 2226-35

37. WHO. Cancer pain relief, 2nd Edn. Geneva, Switzerland: World Health Organization, 1996.

38. Blinderman CD, JA Billings. Comfort Care for Patients Dying in the Hospital. *N Eng J Med* 2015; 373: 2549-61

39. Bruce RD, Merlin J, Lum PJ, et al. 2017 HIVMA of IDSA Clinical Practice Guidelines for the Management of Chronic Pain in Patients Living with HIV. *Clin Infect Dis* 2017; 65(10):e1-3

40. Portenoy RK. Treatment of cancer pain. Lancet 2011; 377: 2236-47

41. Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *N Engl J Med* 2016; 374; 154-63

42. Knaul FM, Farmer PE, Krakauer EL, et al. on behalf of the Lancet Commission on Palliative Care and Pain relief Study Group. Alleviating the access abyss in palliative care and pain relief - an imperative of universal health coverage: the Lancet Commission Report. *Lancet* 2018; 391: 1391-454

43. Chang E, Sekhar R, Patel S, Balasubramanyam A. Dysregulated Energy Expenditure in HIV-Infected Patients: A Mechanistic Review. *Clin Infect Dis* 2007; 44: 1509-17

44. Mangili A, Murman DH, Zampini AM, Wanke CA. Nutrition and HIV Infection: Review of Weight Loss and Wasting in the Era of Highly Active Antiretroviral Therapy from the Nutrition for Healthy Living Cohort. Clin Infect Dis 2006; 42: 836-42

45. Argemi X, Dara S, You S, et al. Impact of malnutrition and social determinants on survival of HIV-1 infected adults starting antiretroviral therapy in resource-limited settings. *AIDS* 2012; 26: 1161-66

46. Rabkin JG, Wagner GJ, Rabkin r. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. Arch Gen Psychiatry 2000; 57: 141

47. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet 2008; 371: 1364-74

48. Walzer PD, Evans HER, Copas AJ, et al. Early Predictors of Mortality from *Pneumocystis jirovecii* Pneumonia in HIV-Infected Patients: 1985-2006. *Clin Infect Dis* 2008; 46: 625-33

49. Powell K, Davis JL, Morris AM, et al. Survival for Patients With HIV Admitted to the ICU Continues to Improve in the Current Era of Combination Antiretroviral Therapy. *Chest* 2009; 135(1):11-17

50. WHO 2014 Consolidated Guidelines. Prevention, Screening and Management of Common co-infections. Section 5.2 Pg. 28. Co-trimoxazole Prophylaxis for Adults

51. Insight START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med* 2015; 373; 795-807

52. Hesketh PJ. Chemotherapy-Induced Nausea and Vomiting. N Engl J Med 2008; 358: 2482-94

53. Nakagawa S, Toya Y, Okamoto Y, et al. Can anti-infective drugs improve the infection-related symptoms of patients with cancer during the terminal stages of their lives? *J Palliat Med* 2010; 13: 535-40

54. Eggers C, Arendt G, Hahn K, et al., for the German Association of Neuro-AIDS und Neuro-Infectiology (DGNANI). HIVC-1 –associated neurocognitive disorder: epidemiology, pathogenesis, diagnosis and treatment. *J Neurol* 2017; 264: 1715-1727

55. Eden A, Fuchs D, Hagberg L, et al. HIV-1 Viral Escape in Cerebrospinal Fluid of Subjects on Suppressive Antiretroviral Treatment. J Infect Dis 2010; 202(12): 1819-1825

56. Goldberg DW, Tenforde MW, Mitchell HK, Jarvis JN. Neurological Sequelae of Adult Meningitis in Africa: A Systematic Literature Review. Open Forum Infect Dis 2017; DOI:10.1093/ofid/ofx246.

57. Siddiqi OK, Ghebremichael M, Dang X, et al. Molecular Diagnosis of Central Nervous System Opportunistic Infections in HIV-Infected Zambian Adults. *Clin Infect Dis* 2014; 58(12): 1771-7

58. Britz E, Perovic O, von Moolendorf C, et al. The Epidemiology of Meningitis among Adults in a South African Province with a High HIV Prevalence, 2009-2012. *PloS ONE* 2016; 11(9): e0163036. Doi:10.1371/journal.pone.0163036

59. Molloy SF, Kanyama C, Heyderman RS, et al., for the ACTA trial Study Team. Antifungal Combinations for treatment of Cryptococcal Meningitis in Africa. *N Engl J Med* 2018; 378: 1004-17

60. Kingham TP, Alatise OI, Vanderpuye V, et al. Treatment of Cancer in sub-Saharan Africa. *Lancet Oncol* 2013; 14: e158-67.

61. Livingston J. Cancer in the Shadow of the AIDS Epidemic in Southern Africa. *The Oncologist* 2013; 18: 783-86

62. Dryden-Peterson S, et al. Malignancies among HIV-infected and HIV-uninfected patients in a Botswana prospective cohort. Poster 902. The 19th Conference on Retroviruses and Opportunistic Infections, Seattle, Washington, March 5-9, 2012

63. Stein L, Urban MI, O'Connell D, et al. The spectrum of human immunodeficiency virus-associated cancers in a South African black population: Results from a case-control study, 1995-2004. *Int J Cancer* 2008; 122: 2260-2265

64. Chinula L, Moses A, Gopal S. HIV-associated malignancies in sub-Saharan Africa: progress, challenges, opportunities. *Curr Opin HIV AIDS* 2017; 12(1): 89-95

65. Deeken JF, Tjen-A-Loon A, Rudek MA, et al. The Rising Challenge of Non-AIDS-Defining Cancers in HIV-Infected Patients. *Clin Infect Dis* 2012; 55(9): 1228-35

66. Coleman MP. Cancer survival: global surveillance will stimulate health policy and improve equity. *Lancet* 2014; 383: 564-73

67. Yarchoan R, Uldrick TS. HIV-Associated Cancers and related Diseases. *N Eng J Med* 2018; 378: 1029-41

68. Bruyand M, Thiebaut R, Lawson-Ayayi S, et al., for the Groupe d'Epidemiologie Clinique du Sida en Aquitaine (GECSA). Role of Uncontrolled HIV RNA Level and Immunodeficiency in the Occurrence of Malignancy in HIV-Infected Patients during the

Combination Antiretroviral Therapy Era: Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort. *Clin Infect Dis* 2009; 1109-16

69. Bonnet F, Balestre E, Thiebaut R, et al. for the Groupe d'Epidemiologie Clinique du SIDA en Aquitaine. Factors Associated with the Occurrence of AIDS-Related Non-Hodgkin Lymphoma in the Era of Highly Active Antiretroviral Therapy: Aquitaine Cohort, France. *Clin Infect Dis* 2006; 42: 411-7

70. Torres HA, Mulanovich V. Management of HIV Infection in Patients With Cancer Receiving Chemotherapy. *Clin Infect Dis* 2014; 59(1): 106-14

71. Bateganya MH, Stanaway J, Bretlinger PE, et al. Predictors of Survival after a Diagnosis of Non-Hodgkin Lymphoma in a Resource-Limited Setting. *J Acquir Immune Defic Syndr* 2011; 56(4): 312-319

72. Cyr C, Arboleda MF, Kumar S, et al. Cannabis in palliative care: current challenges and practical recommendations. *Ann Palliat Med* 2018; doi.21037/apm.2-18.06.04. View at http://dx.doi.org/10.21037/apm.2018.06.04

73. Bar-Lev Schleider L, Mecholam R, Lederman V, et al. Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer. *Eur J Intern Med* 2018; 49: 37-43

74. Manuzak JA, Gott TM, Kirkwood JS, et al. Heavy Cannabis Use Associated With Reduction in Activated and Inflammatory Immune Cell Frequencies in Antiretroviral Therapy-Treated Human Immunodeficiency Virus-Infected Individuals. Clin Infect Dis 2018 Jun 1; 66(12): 1872-1882. Doi.10.1093/cid/cix1116.

75. Ferry G. Thomas Browne: a rarity among rarities. *Lancet* 2017; 389: 1687-88

76. Csete J, Kamarulzaman A, Kazatchkine M, et al. Public health and international drug policy. Lancet 2016; 387: 1427-80.

77. Editor. Progressive interventions needed to stem medical litigation 'explosion'. The Medical Brief. Africa's Medical Media Digest. April 18, 2018. Accessed at, https://www.medicalbrief.co.za/archives/progressive-interventions-needed-stem-medical-litigation.

78. Editor. Mpumalanga and Eastern Cape face R10.9bn in medical negligence claims. The Medical Brief. Africa's Medical Media Digest. June 13, 2015. Accessed at, https://www.medicalbrief.co.za/archives/mpumalanga-eastern-cape-face-r10-9bn-medical-negligence-claims.

APPENDIX A. PALLIATIVE CARE MODEL: NO CARE

Characteristics of this model include:

- **Acute hospitalisation**
  - Even when seriously ill, palliative care and support are generally not offered in public or private hospitals in South Africa
  - Primary attention is directed to acute and curative care
  - Care is seldom team work; Each caregiver works independently and very few have had formal training in palliative care
  - The public health system's masterplan is usually focused on early discharge and the emptying of beds in preparation for the next intake of acutely ill patients.
  - Patients are seldom, if ever, asked about their end-of-life thoughts or wishes
  - Families rarely participate in the provision of the patient's care
  - The day to day care provided in many of SA's public hospitals is given by junior doctors, e.g. community service doctors, interns, medical officers, registrars etc., particularly in district and rural hospitals. Supervision is not uniform and senior consultants in public hospitals are seldom in the wards every day and less often in the evenings and at night.

- **The HIV-patient**
  - **Patient characteristics.** Many patients are newly diagnosed or previously diagnosed and started on ART but had been lost to follow-up. The presentation is diverse: Comorbid conditions, e.g. diabetes, renal failure, hepatitis B etc., AIDS-defining and non-AIDS defining diseases, e.g. community acquired pneumonia (CAP), pneumocystis pneumonia (PJP), etc., anaemia, low platelets, gastroenteritis, ART-associated toxicity and treatment failure (viral resistance) etc. Occasionally the primary presentation is with a condition not immediately associated with HIV, e.g. trauma, malaria, skin rash, etc. Often patients are very ill and the mortality rate is substantial.
  - **Tuberculosis** (TB) is frequent, needs to be excluded in all and is the major cause of death. Care requires attention to symptomatic control (palliation), curative therapy and the prevention of transmission.
  - **Poverty and limited social resources with adherence problems**. Non-disclosure to family members is frequent, stigma dictates behaviour and non-disclosure results in non-adherence which leads to treatment failure. Neuro-cognitive dysfunction is common and may contribute to non-adherence (forgetfulness) and unreliable clinic attendance of some. The care of the HIV-infected needs to be broad-based to ensure that social, psychological and practical needs are met.
  - **The HIV-sick**. Many patients present with >1 major diagnosis, e.g. TB and bacterial pneumonia, PJP and renal failure, Kaposis's sarcoma (KS) and bacteremia etc., and multiple concurrent diagnoses increase mortality. ARVs are toxic and drug-drug interactions are frequent and occasionally life-threatening, e.g. drug-induced liver injury (DILI), Stevens Johnson syndrome (SJS) and erythema multiforme (EM).

- **Laboratory indices**
  - **Baseline HIV diagnostic tests** (HIV antibody tests) are still not performed on all who are admitted to SA private and public hospitals. HIV-directed care, e.g.

ARVs, cannot be given without this baseline information. Only ART can control HIV infection.
    - **CD4 counts** are often low in this group of patients, e.g. <200 cells/mm^3, and patients are vulnerable to a variety of opportunistic diseases.
    - **Viral load.** The SA National ART guidelines discourage checking a patient's **viral load (VL)** at the time of the baseline assessment, but recommend that the VL is checked 6 months after starting ART and annually thereafter. Elevated VL = adverse survival if on ART. Persistently high VL = increased risk of cancer in the HIV-infected.
    - **Markers of mortality**: Anaemia (Hb. <8 g/dl), CD4 <200 cells/mm^3, VL (esp. >100,000 copies/ml), end-organ failure (renal, liver), a low body mass index (BMI <18 Kg/m^2).
    - **Delay in laboratory turn-around times.** Histology results appear particularly resistant to short turn-around times yet the care of **the HIV-cancer patient** depends upon tissue confirmation. Patients without timeous results do not get chemotherapy, do not start ART early enough and do not survive.

- **Radiology**
    - Access to ultrasound, echocardiography, CT and MRI scans etc., in the government sector and especially in rural and secondary level hospitals is poor and delays in obtaining these tests are widespread, even in larger public hospitals.
    - Transfer to referral centres is difficult to expedite: Transport is not always readily available and permission is needed, as is the willingness of the referral hospital to accept the patient.

- **Medical team**
    - The care of the HIV-well is spelled-out in guidelines. The care of the HIV-sick requires practical training and the acquisition of bedside skill, as good palliative care will require a command of the care of the HIV-sick.
    - Junior doctors, e.g. community-service, interns and registrars, carry a major responsibility in the day-to-day provision of patient care in SA's public hospitals. Additional training will be needed to equip junior staff on how to triage between the curative and palliative disciplines of care and the combinations of both.

- **Dying in a South African public hospital**
    - Terror. Loneliness. Abandonment. Pain. Suffering. Family often absent at the time of death. The 'End-of-life' discussion occurs rarely, if at all, and the family often feels left-out and aggrieved, and regret occurs as seldom the gathering together of loose ends takes place during the contented arrival of life's end.

- **Bereavement counselling**
    - Usually none given to the patient or family before or after death. Questions of the bereaved are often left unaddressed and anger and disappointment are seldom addressed. Litigation is an option for the disgruntled family.

APPENDIX B. INDICATORS OF INCREASED MORTALITY OF HIV-INFECTED PATIENTS

Demographic indicators of an increased risk of death:

- Age ≥45-50 years old. Risk increases with age and includes risk from comorbid disease. Male gender is frequently associated with increased risk but confounded by late entry into care, poor retention in care, lower baseline CD4 cell counts and older age at entry than females.

Clinical indicators of an increased risk of death:

- Unintended weight loss of >10% normal body weight, and/or body mass index (BMI) ≤18 kg/m^2.
- AIDS-defining clinical conditions yet the risk is not the same for all events. TB, cryptococcal meningitis (CM) and malignancy in Africa carry a higher risk than other AIDS-defining conditions.
- AIDS and non-AIDS defining cancers in the HIV-infected.
- Comorbid disease and end-organ failure: Renal, liver, cardiac and respiratory.
- Confirmed ARV-resistance, particularly high-level resistance to all major classes of ARV.
- Hospital re-admission rates and Grip Strength. Thirty-day hospital readmission rates in HIV-positive adults are associated with other markers of poor outcome viz. low CD4 counts, AIDS-defining illnesses, non-AIDS defining infections and unreliable utilisation of medication.

Laboratory indicators of an increased risk of death:

- CD4 count: CD4 ≤200c/mm^3 or lower. The lower the level, e.g. <50c/mm^2, the greater the risk.
- Anaemia: particularly if severe viz. Hb <8g/dl.
- HIV viral load: High levels viz. >100,000 copies/mL prior to ART, and detectable levels while on ART. The higher the level, the greater the risk, e.g. malignancy.

Combination indicators of an increased risk of death:

- The Veterans Aging Cohort Study (VACS) Index. This developed-world (US) scoring system incorporates seven clinical/laboratory indices that, taken together, predict death in HIV-infected persons. Several observational reports indicate that this index has superior predictive value to both single and composite indices currently in use. The role of Hepatitis C virus positivity in the VACS scoring system is numerically small and unlikely to negatively influence its utility in southern Africa where the prevalence of HCV is low, i.e. 3-5%.

APPENDIX C. THE KARNOFSKY SCORE

The Karnofsky score was developed in 1948, enabling physicians to evaluate a patient's ability to survive cancer chemotherapy. It is still in general use, however, its insensitivity and non-specificity with regard to HIV-infected patients limit its use in deciding on access to hospice-related care.

- 100 – Normal; no complaints; No evidence of disease
- 90 – Able to carry on normal activity; Minor signs or symptoms of disease
- 80 – Normal activity with effort; Some signs or symptoms of disease
- 70 – Cares for self; Unable to carry on normal activity or to do active work
- 60 – Requires occasional assistance, but is able to care for most of their personal needs
- 50 – Requires considerable assistance and frequent medical care
- 40 – Disabled; Requires special care and assistance
- 30 – Severely disabled; Hospital admission is indicated although death not imminent
- 20 – Very sick; Hospital admission necessary; Active supportive treatment necessary
- 10 – Moribund; Fatal processes progressing rapidly
- 0 – Dead

Ref. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The Use of the Nitrogen Mustards in the Palliative Treatment of Carcinoma – with Particular Reference to Bronchogenic Carcinoma. *Cancer.* 1948; 1(4):634-56

APPENDIX D. THE SUPPORT AND PALLIATIVE CARE INDICATOR TOOLS (SPICT^{TM})

The SPICT^{TM} is a guide for identifying people at risk of deteriorating health and imminent death. This group of patients must be assessed for unmet supportive and palliative care needs.

(i) Look for two or more general indicators of deteriorating health:

- Performance status is poor or worsening, i.e. the person is in bed or in a chair for ≥50% of the day; Reversibility is judged as limited
- Dependent on others for most care needs; Dependency is due to physical and/or mental health problems
- Two or more unplanned hospital admissions in the past 6 months
- Significant weight loss (5-10%) over the past 3-6 months, and/or a low body mass index, i.e. BMI <18kg/m^2
- Persistent, troublesome symptoms despite optimal treatment of underlying conditions
- Patient asks for supportive and palliative care or for the withdrawal of treatment

(ii) Look for any clinical indicators of one or more advanced conditions:

Cancer:
- Functional ability deteriorating due to progressive metastatic cancer
- Too frail for oncology treatment or treatment is for symptom control only

Dementia/frailty:
- Unable to dress, walk or eat without help
- Eating and drinking less; Swallowing difficulties
- Urinary and faecal incontinence
- No longer able to communicate using verbal language; Minimal social interaction
- Fractured femur; Multiple falls
- Recurrent febrile episodes or infections; Aspiration pneumonia

Neurological disease:
- Progressive deterioration in physical and/or cognitive function despite optimal therapy
- Speech problems with increasing difficulty communicating and/or progressive swallowing difficulties
- Recurrent aspiration pneumonia; Breathless or respiratory failure

Heart and/or vascular disease:
- NYHA Class III/IV heart failure or extensive, untreatable coronary artery disease with –
    - Breathlessness or chest pain at rest or on minimal exertion
- Severe, inoperable peripheral vascular disease

Respiratory disease:
- Severe chronic lung disease with –
    - Breathlessness at rest or on minimal exertion between exacerbations
- Needs long-term oxygen therapy
- Has needed ventilation for respiratory failure or in whom ventilation is contraindicated

Kidney disease:

- Stage 4 or 5 chronic kidney disease viz. an eGFR <30 mL/min, with deteriorating health
- Kidney failure complicating other life limiting conditions or treatments
- Discontinuation of dialysis

Liver disease:

- Advanced cirrhosis with one or more complications in the past year –
  - Diuretic resistant ascites
  - Hepatic encephalopathy
  - Hepatorenal syndrome
  - Bacterial peritonitis
  - Recurrent variceal bleeds
- Liver transplantation is contraindicated

What to do: Review supportive and palliative care planning:

- Review current treatment and medication so that the patient receives optimal care
- Consider referral for specialist assessment if symptoms or needs are complex and difficult to manage
- Agree to current and future care goals and a care plan with the patient and his/her family
- Plan ahead if the patient is at risk of loss of capacity
- Record, communicate and coordinate the care plan

Ref. The Support and Palliative Care Indicator Tools (SPICT^{TM}). University of Edinburgh, SPICT^{TM}, April 2015, www.spict.org.uk.

APPENDIX E. THE ESTABLISHED VACS INDEX SCORING SCHEME

The VACS Index utilises age, routine laboratory markers such as CD4 count, HIV-1 RNA, haemoglobin, platelets, AST and ALT, creatinine and markers of liver impairment viz. FIB-4 and HCV status.

* FIB-4 = age (yr) X AST/ platelet in 100/L X √ALT

** eGFR = 186.3 X (creatinine) $^{-1.154}$ X (age) $^{-0.203}$ X (0.742 for women) X (1.21 for Black individuals)

Component	Level	VACS Index Points Assigned
Age (years)	<50	0
	50-64	12
	≥65	27
CD4 count (cell/mm^3)	≥500	0
	350-499	6
	200-349	6
	100-199	10
	50-99	28
	<50	29
Viral load (copies/mL)	<500	0
	500-log1 x10^5	7
	≥log1 x 10^5	14
Haemoglobin (g/dL)	≥14	0
	12-13.9	10
	10-11.9	22
	<10	38
***FIB-4**	<1.45	0
	1.45-3.25	6
	>3.25	25
eGFR (mL/min)	≥60	0
	45-59.9	6
	30-44.9	8
	<30	26
Hepatitis C co-infection	YES	5
	NO	0

Ref: Tate JP, Justice AC, Hughes MD, et al. The VACS Index: An internationally generalizable risk index for mortality after one year of antiretroviral therapy. AIDS 2013; 27(4): 563-572 doi:1-/1097/QAD.06013e32835b8c7f.

APPENDIX F. PALLIATIVE CARE MANAGEMENT

Drugs Used for Symptom Control in HIV Palliation

Abbreviations:

ATV/r	Atazanavir/ritonavir
AZT (ZDV)	Azidothymidine (zidovudine)
bPI	Boosted protease inhibitors
DTG	Dolutegravir
EFV	Efavirenz
EI	Entry inhibitors (Maraviroc, **MVC**)
ETR	Etravirine
FTC	Emtricitabine
INSTI	Integrase strand-transfer inhibitors
NNRTI	Non-nucleoside RTI
NRTI	Nucleoside/tide reverse transcriptase inhibitors
NVP	Nevirapine
RAL	Raltegravir
RPV	Rilpivirine
TDF	Tenofovir disoproxil fumarate

Appendix F (i). Palliative Care Management, Drug-Drug Interactions

Symptom	Palliative Drug Treatment	Antiretroviral Interaction	Potential Hazards
Constitutional			
Fatigue and Weakness:	Where possible treat the underlying cause and not just the symptom		
	Corticosteroids	EI: None NRTI: None NNRTI (CYP450 enzyme induction): Minor interaction INSTI: None Boosted PI (bPI) (CYP450 inhibition): Potential interaction	Long term co-administration with bPIs = potential toxicity of steroid viz. Cushing's Syndrome and additional deterioration of immune state
	Methylphenidate	None	None
	Pemoline	None	None
	Dextroamphetamine	EI: None NRTI: None NNRTI: None INSTI: None with RAL and DTG, but avoid with EVG/ cob +TDF+FTC bPI: None	Likely potentiation of amphetamine toxicity with EVG/cobicistat: Avoid or use with caution

	Modafinil	EI: Interaction likely with MVC NRTI: None NNRTI: Potential interaction INSTI: None bPI: Potential interaction	Modafinil=mild enzyme induction; Do not use with RIL and caution with NVP; Potential increased drug (Modafinil) toxicity with the bPIs: Use with caution
Weight Loss and Anorexia:	Where possible treat the underlying cause and not just the symptom		
	Corticosteroid		As above
	Androgenic steroids	As for steroids above EI: None NRTI: None NNRTI: None INSTI: None bPI: Small potential for toxicity	Long term use = potential for androgenic excess (toxicity) with long term use of bPI
	Oxandrolone	None	None
	Megestrol acetate	None	None
	Dronabinol	EI: None NRTIs: None NNRTIs: EFV and ETR= Caution INSTI= None bPIs= potential decrease in activity of dronabinol	EFV and ETR inhibit CYP2C9 and to a lesser extent 3A4=increase dronabinol toxicity; Ritonavir is a mild enzyme inducer = reduce dronabinol activity
	Growth Hormone (GH): recombinant	None	
Fever/Sweats ++:	Where possible treat the underlying cause and not just the symptom.		
	NSAIDS: Anti-inflammatory effect	EI: None NRTIs: None NNRTIs: Use lowest dose of aspirin, ibuprofen etc.to start. INSTIs: None bPIs: None	EFV and ETR inhibit CYP2C9 =potential for bleeding: Caution NB. Note renal and bleeding/platelet dysfunction risk with NSAIDS: Caution with TDF and background renal disease
	Corticosteroids	As above	
	Anticholinergics, e.g. diphenhydramine, biperiden, chlorpromazine etc.	EI: None NRTIs: None NNRTIs: None INSTIs: None bPIs: Caution	bPIs block CYP2D6 and may inhibit the metabolism of many anti-cholinergic drugs; Monitor patient carefully
	H2 Antagonists, e.g. cimetidine, ranitidine etc.	EI: None NRTIs: None NNRTI: Caution with RIL	NB; Reduced absorption of H2 antagonists, e.g. ranitidine, in the absence of gastric acid; Give RIL 4h before ranitidine or 12h

		bPI: Caution with ATV Must give max dose 400mg ATV+ 100mg ritonavir if using TDF backbone!	after; In presence of TDF always give boosted ATV/r as absorption is otherwise compromised
Gastrointestinal			
Nausea and Vomiting:	Where possible treat the underlying cause and not just the symptom.		
Drug-related. Dopamine antagonists.	Haloperidol	EI: None NRTIs: None NNRTIs: Caution INSTIs: None bPIs: Caution	Haloperidol levels decreased with NVP, EFV and ETR; Potential for prolongation of QT interval with RIL, haloperidol and the PIs = risk of Torsáde de Pontes
	Prochlorperazine	EI: None NRTIs: Caution. Risk of marrow suppression with AZT (ZDV) and prochlorperazine NNRTIs: Caution bPI: Caution	Caution: Risk of QT prolongation with prochlorperazine, RIL and bPIs; ECG monitoring recommended
Opiate side-effect	Metoclopramide	None	
Distention of the GIT	Antihistamines: Promethazine	EI: None NRTI: None NNRTI: None INSTI: None bPI: Caution, potential toxicity	Promethazine metabolized via CYP2D6; If inhibited, may potentiate toxicity.
GIT Obstruction	Anticholinergics: Scopolamine and hyoscine		
Raised Intracranial Pressure (RIP)	Corticosteroids	As above	As above
Post-chemotherapy; Post-radiotherapy; Post-operative	Serotonin-antagonists: Granisetron, ondansetron and dolasetron	EI: None NRTI: None NNRTI: Caution with all, but watch for QT interval prolongation with RIL: Caution INSTI: none bPI: May potentiate toxicity. Caution.	All metabolized via CYP3A4; All NNRTIs may decrease levels; RIL, granisetron/ ondansetron prolong QT interval; bPIs potentiate toxicity of these agents.
Pre-vomit anxiety	Benzodiazepines, e.g. lorazepam	EI: None NRTI: None	Co-administration of bPI with midazolam may

		NNRTI: None INSTI: None bPI: Avoid with midazolam, oxazepam and lorazepam - Safe	potentiate toxicity and result in fatal respiratory suppression
Diarrhea:	Where possible treat the underlying cause rather than just the symptom		
	Bismuth	None	None
	Methylcellulose	None	None
	Kaolin	None	None
	Diphenoxylate + atropine	None	None
	Octreotide	EI: None NRTI: None NNRTI: Caution INSTI: None bPI: Caution	Octreotide utilises CYP3A4: NNRTI is expected to decrease octreotide levels; bPI use is expected to enhance toxicity of octreotide
	Opiate	As above	None
	Lactulose	None	None
	Senna	None	None
	Bisacodyl	None	None
Respiratory:	Where possible treat the underlying cause and not just the symptom		
Dyspnoea			
	Opioids	As above	Above
	Bronchodilators	None	None
	Methylxanthines	None	None
	Benzodiazepines	As above	As above
Cough			
Suppressants	Opioids: Codeine, dextromethorphan	As above	As above
	Decongestants	None	None
	Expectorants	None	None
Increased oral and upper respiratory tract secretions: Usually pre-agonal			
	Atropine	None	None
	Hyoscine	None	None
	Scopolamine: Transdermal	None anticipated	None
	Glyco-pyrrolate	None	None

Appendix F (ii). Palliative Care Seizure Management, Drug-Drug Interactions

Drug	Advantage	Disadvantage	Interaction
Carbamazepine	Effective, low cost	Enzyme inducer	Reduces levels of NNRTI and PI: Avoid
Phenobarbital	Effective, low cost	Enzyme inducer	Reduces levels of NNRTIs and PI: Avoid
Phenytoin	Effective, low cost	Enzyme inducer	Reduces levels of NNRTIs and PI: Avoid
Sodium Valproate	Effective, useful for migraine, mood stabiliser	Enzyme inhibitor	May increase AZT toxicity: Caution; Can be used with other ARVs
Gabapentin	Effective for neuropathic pain	Useful for control of focal seizures	No drug-drug interactions
Lamotrigine	Effective against focal and generalised seizures, help with bipolar depression	Effective against all types of seizure	Susceptible to enzyme inducers, e.g. rifampicin: Caution
Levetiracetam	Effective, well tolerated, more expensive	Useful for all types of seizure	No drug-interactions

Appendix F (iii). Palliative Care Pain Management, Drug-Drug Interactions.

Pain Medication	NRTIs	NNRTIs	INSTIs	PIs
Non-opioid				
Paracetamol	No specific ARV interaction anticipated; Watch liver function particularly when using TB-drugs, NNRTIs (NVP and EFV) and bPIs; Active hepatitis - Avoid paracetamol			
NSAID: Ibuprofen	No specific ARV interaction; Watch renal function and bleeding risk (platelet dysfunction)			
Opioid analgesics				
Codeine	No specific interaction anticipated with EIs, NRTIs and INSTIs; Risk of decreased opiate activity with NNRTI interaction is minimal; Similarly, the risk of potentiation of opiate compounds with boosted PIs is likely to be small; Nevertheless, caution is advised when using a bPI with opioids			
Dihydrocodeine				
Tramadol				
Morphine				
Oxycodone				
Adjuvant analgesics				
Tricyclic antidepressants				
Amitriptyline	None	RPV= QT interval prolongation	None	Possible risk: Enhanced toxicity of amitriptyline
Desipramine	None	RPV= Enhanced toxicity, QT prolongation	None	Possible risk of toxicity
Selective Serotonin/noradrenalin reuptake (SNRIs): Duloxetine/ Venlafaxine	None	None	None	Caution: Possible risk of toxicity
NMDA receptor antagonists – Ketamine	None	Caution: May decrease ketamine levels	None	Caution: May enhance ketamine toxicity
Pregabalin	None	None	None	None
Gabapentin	None	None	None	None

NOTES:

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